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THE CHANGES IN THE BLOOD AND HÆMATOPOIETIC TISSUE IN EXPERIMENTAL LEAD POISONING.[1]

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SINCE ancient times the effect of lead poisoning in producing an anæmia has been observed. Allusions to the pallor of the skin are found in various classical and semi-classical writings. Vitruvius[1] writing two thousand years ago described the peculiar complexion of lead workers: "They are a pallid colour, for in casting lead the fumes from it, fixing on the different members and daily burning them, destroy the vigour of the blood." Nicander[2] who in 100 B.C. wrote a poem on poisons and their antidotes, noted among other symptoms "the livid paleness of the complexion" and Discorides[3] who lived in the first century, also described the "unsightly leaden hue" of the complexion in lead poisoning.

With the coming of the industrial era in the last century the incidence of lead poisoning increased proportionately and the subject has assumed an importance which is reflected in an extensive literature. In 1831 Laennec[4] described the pallor of the tissues and the thinness of the blood found at autopsy in cases of plumbism. In 1840 Andral and Gervanet[5] were the first to count the red blood corpuscles in lead poisoning and they found the count to be much lower than normal.

Heubel,[6] in 1871, finding increased pigment in serum, bile and urine, suggested that the anæmia was due to a destruction of the red cells in the circulating blood.

Punctate basophilia was first described by Ehrlich[7] in 1885 and its association with lead poisoning was pointed out by Behrend[8] in 1889.

Agasse-Lafont and Heim[9] in 1910, von Liebermann[10] in 1912, and more recently in 1924 Aub, Reznikoff and Smith[11] have shown that lead in-

[1] Read at a meeting of the Victorian Branch of the British Medical Association on March 5, 1930.

creases the resistance of red cells to hypotonic saline solution. Aub, Reznikoff and Smith[12] have also demonstrated in a series of *in vitro* experiments that red cells treated with lead do not become agglutinated when treated with appropriate group sera and that they show an increased specific gravity and a loss of stickiness of the cell surface.

The presence of various pigments derived from hæmoglobin in serum, bile and urine is evidence of the abnormal destruction of red blood corpuscles. Hæmatoporphyrin is found in urine and fæces in cases of lead poisoning (Liebig[13]). Brady[14] demonstrated marked hæmaturia and an increase in the excretion of bile pigments from the common bile duct in rabbits poisoned with lead acetate. Increased pigment in the spleen has been observed as a frequent result of lead poisoning (Jores,[15] Seiffert and Arnold[16]). Brookfield[17] observed an icteric tinge in the complexion of patients after receiving injections of colloidal lead and a positive indirect Van den Bergh reaction and excess of urobilin in the urine was demonstrated.

There is a difference of opinion amongst authorities as to the changes in the white blood cells in lead poisoning. According to Legge and Goadby[18] there is in acute lead poisoning a distinct leucocytosis and this is manifest as an increase in the number of lymphocytes and large mononuclears, while there is a decrease in the percentage of polymorphonuclear cells.

On the other hand, Aub, Fairhall, Minot and Reznikoff,[19] in their differential counts, find no increase in the total number of mononuclear cells and Blair Bell, Williams and Cunningham[20] find in patients treated with colloidal lead injections for malignant disease, that "there is nothing specific or definite in regard to the change seen in white cells."

With regard to changes in the hæmatopoietic tissue in lead poisoning comparatively little work has been done. Raimondi[21] in 1880 poisoned three rabbits with lead acetate and found that the fat had disappeared from the bone marrow and that it was in a condition of gelatinous degeneration. Stockman and Charteris[22] in lead poisoned rabbits observed an early increase in leucoblast cells with a disappearance of the fat cells, which was followed by a gelatinous degeneration with atrophy of the whole marrow tissue. In chronic lead poisoning in rabbits Jores[15] observed increased pigment in the bone marrow with almost complete disappearance of the fat cells, but otherwise he says the structure of the bone marrow was not much changed. Ophuls[23] reports in lead poisoned guinea-pigs an excessive number of nucleated red cells in the bone marrow. Seiffert and Arnold[16] examined blood, bone marrow and spleen in experimental lead poisoning in guinea-pigs and observed degenerative changes in monocytes, increased formation of red cells in bone marrow and evidence of increased cell destruction in spleen, particularly of nucleated red cells.

It would appear that much experimental work and much clinical investigation have been devoted to the study of the effect of lead on the blood. That it has a particular and probably a specific action on the red cells is undoubted, but as to the *modus operandi* very little is known. A field which has been neglected in the study of lead poisoning, is the correlation of the changes in the peripheral blood cells and in the hæmatopoietic tissue. Another phase of lead anæmia which has received scant attention, is the effect on blood volume. When it is considered that lead has a toxic effect on the kidneys as well as on the blood, the question arises as to what extent the anæmia is due to a depletion of corpuscular volume resulting from red cell destruction or to an increase in plasma volume possibly due to kidney inefficiency. That the white blood cells are characteristically affected by lead is admitted by some workers and denied by others and, as far as can be ascertained from the literature, very little work has been done on the variation in the platelet count in lead poisoning.

An attempt has been made to investigate these problems and changes in red blood cells, blood volume, leucocytes, platelets, bone marrow, spleen and lymph glands in experimental acute lead poisoning in rabbits have been studied.

Changes in Red Blood Corpuscles, Hæmoglobin and Reticulocytes Following upon Intravenous Injections of Colloidal Lead.

Method.

Australian wild rabbits were used in all the experiments. Colloidal lead was prepared according to the method described by Blair Bell[24] and was used immediately after preparation. In the red cell counts a Thoma-Zeiss hæmocytometer was used and two marked pipettes were used for each enumeration, the same pipettes being used for the same rabbit throughout the experiment. An average of two to four counts was taken, and all the counts were made by the author. Brookfield's method for counting reticulocytes was employed, using 0·3% brilliant cresyl blue in citrated saline solution and a thousand cells were counted in each estimation. Hæmoglobin was estimated by Sahli's method. Blood films were made in the usual way and stained with Giemsa (Grübler).

Results.

The changes in red cell count, hæmoglobin, reticulocytes and the appearance of stippling following the intravenous injections of colloidal lead in five rabbits are shown in Table I.

There is a marked fall in the red cell count after each injection and this reduction in the number of red blood corpuscles is greater with the larger doses of lead. The percentage fall in red cell count in the five rabbits with increasing doses of lead is 8%, 17%, 34%, 36% and 31% respectively. Although the fall is greater with the larger doses of lead, the percentage fall in rabbits receiving the same dose of lead per kilogram body weight varies considerably, and there is no obvious relationship between the dose of lead and the extent of anæmia produced.

TABLE I.

Rabbit.	Weight in Grammes.	Date.	Colloidal Lead per Kilogram Bodyweight in Milligrammes.	Red Blood Cells in Millions per Cubic Millimetre.	Hæmoglobin (Sahli).	Reticulocytes, Percentage.	Stippled Cells, Percentage.
I	1,320	3/10/28	—	6·08	67	1·1	—
		P.M.	22·5	—	—	—	—
		5/10/28	—	5·60	52	0·7	6·3
		10/10/28	—	5·50	47	2·4	1·8
		P.M.	22·5	—	—	—	—
		12/10/28	—	4·80	47	3·9	0·7
		17/10/28	—	5·20	46	8·0	1·1
		18/10/28	22·5	—	—	—	—
		20/10/28	—	4·70	48	3·7	2·6
		24/10/28	—	4·50	45	12·0	6·5
		26/10/28	—	4·30	47	14·7	1·4
		29/10/28	—	3·70	45	14·5	—
II	1,380	3/10/28	—	5·20	63	3·5	—
		P.M.	30·0	—	—	—	—
		5/10/28	—	4·30	47	5·0	0·5
		10/10/28	—	4·00	44	25·0	1·2
		P.M.	30·0	—	—	—	—
		12/10/28	—	3·80	42	17·2	6·7
		17/10/28	—	5·20	46	8·0	1·1
		18/10/28	30·0	—	—	—	—
		20/10/28	—	4·30	37	6·2	—
		24/10/28	—	4·40	40	7·5	1·4
		26/10/28	—	4·50	40	11·8	0·7
		29/10/28	—	4·80	36	8·0	—
		30/10/28	Death	—	—	—	—
III	1,420	3/10/28	—	7·00	62	2·2	—
		P.M.	30·0	—	—	—	—
		5/10/28	—	4·60	48	4·3	0·5
		10/10/28	—	4·10	43	13·0	0·6
		17/10/28	—	4·30	40	8·4	—
		20/10/28	—	5·00	47	9·3	—
			Death				
IV	1,430	3/10/28	—	7·60	72	1·9	—
		P.M.	37·5	—	—	—	—
		5/10/28	—	4·80	45	1·0	0·7
		10/10/28	—	3·70	45	8·5	1·3
		P.M.	37·5	—	—	—	—
		12/10/28	—	4·80	47	3·9	0·7
		17/10/28	—	3·20	27	16·5	1·7
		18/10/28	37·5	—	—	—	—
		20/10/28	—	3·00	26	9·4	2·1
		21/10/28	Death	—	—	—	—
V	1,470	3/10/28	—	8·40	60	1·0	—
		P.M.	37·5	—	—	—	—
		5/10/28	—	5·80	50	1·6	0·3
		10/10/28	—	5·80	48	14·2	—
		P.M.	37·5	—	—	—	—
		12/10/28	—	4·80	43	5·4	0·4
		17/10/28	—	4·40	38	10·6	0·4
		19/10/28	20·0	—	—	—	—
		20/10/28	—	3·50	37	7·3	1·1
		24/10/28	—	3·40	30	5·6	0·6
		26/10/28	—	4·06	33	11·6	1·3
		29/10/28	Death	—	—	—	—

The percentage fall in hæmoglobin in the five rabbits with increasing doses of lead is 22%, 25%, 22% 27% and 17% respectively. This does not correspond with the fall in the red cell count and in all the individual results there is a lack of correlation between the red cell counts and the hæmoglobin, although the mean results (Chart I) run parallel except in the last two examinations.

The reticulocytes do not increase after the injections of lead to an extent corresponding to the reduction in red cells. The increase in reticulocytes which follows a loss of red cells due to hæmorrhage, is demonstrated in the following experiment.

A normal rabbit weighing 1,480 grammes was taken. The red cell count was found to be 5,300,000 per cubic millimetre and reticulocytes 0·3%. Twenty cubic centimetres of blood were withdrawn from the marginal vein of the ear and twenty-four hours later the red cell count was 3,800,000 per cubic millimetre and reticulocytes 4·4%; a further fifteen cubic centimetres of blood were withdrawn and the next day (forty-eight hours after the first bleeding) the red cell count was 3,200,000 per cubic millimetre and reticulocytes 9·0%.

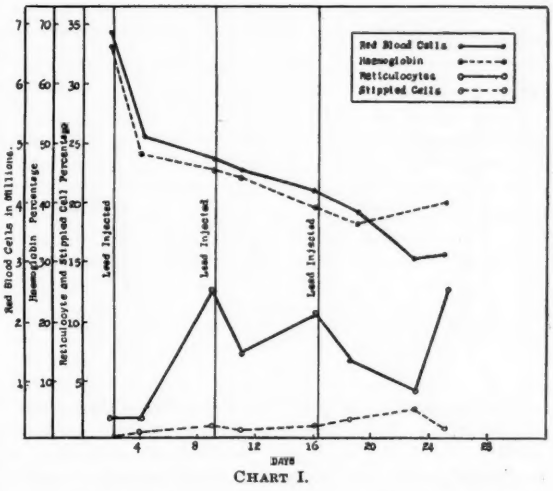

CHART I.

In the lead poisoned rabbits, instead of an increase of reticulocytes, there is a decrease in rabbits I and IV two days after the first dose of lead and only a slight increase in rabbits II and V. With subsequent injections, in every case in which the reticulocytes were present in relatively high percentage, there is a reduction in the number of these cells two days after injection (see Chart I).

Stippling of red cells was observed in blood films from the five rabbits, but the number of stippled cells had no apparent relationship to the number of reticulocytes or to the quantity of lead administered.

The more remote effects of lead on the red cells, hæmoglobin and reticulocytes and the cycle of changes from the normal condition through a phase of anæmia to a condition approximating the normal are demonstrated in the case of rabbit III. This rabbit received a single injection of lead and seven days after the injection developed a paralysis of both posterior extremities. The blood findings are shown in Table I. The usual reduction in red cells and hæmoglobin is evident and is followed, after a practically stationary period of twelve days, by an improvement demonstrated by an increased number of red blood corpuscles per cubic millimetre and a high hæmoglobin figure. Two days after lead injection the reticulocytes had not increased to any marked extent, but five days after lead injection these cells were present in the peripheral circulation in abnormal numbers. Subsequently there was a diminution in the number of reticulocytes.

Anisocytosis of the red cells was a prominent feature of the blood films taken on the second and seventh days after lead injection (Figure I). Polychromatophilia and punctate basophilia were also demonstrated, but poikilocytosis was not marked. Blood films made on the seventeenth day after lead injection showed no apparent abnormality of the

red cells. Price-Jones curves of the red cells from films taken before, two days after, seven days after and seventeen days after the lead injections are shown in Chart II.

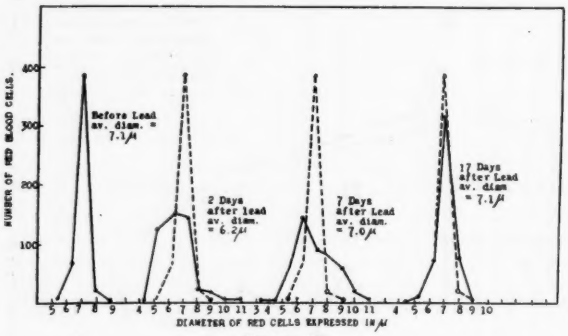

CHART II.

The mean diameter of the red cells in the second and seventh day films was below normal and the curves were typical of secondary anæmia as described by Price-Jones, but there was no marked shift to the left. The nucleated red cells present in the films of all rabbits with lead anæmia were young normoblasts with coarse nuclear chromatin arranged in the typical cartwheel pattern and more mature cells with pyknotic nuclei.

THE EFFECT OF COLLOIDAL LEAD INJECTIONS ON BLOOD VOLUME.

Previous experiments have demonstrated a marked fall in the number of red blood corpuscles per cubic millimetre and in the hæmoglobin following upon intravenous injections of colloidal lead. To determine to what extent this fall is due to destruction of red cells or to a dilution by increased plasma, it is necessary to study blood volume and to observe changes in corpuscular and plasma volumes respectively.

There are one direct and several indirect methods for the determination of blood volume. The direct method was introduced by Welcker[25] in 1854. The animal is bled to death, the vessels are washed out with water and hæmoglobin is extracted from the tissues by mincing and washing. By comparing the hæmoglobin content of the original blood with that of the total blood washings and extractions, Welcker calculated the total blood volume. With this method the blood volume of rabbits was found to be 1/18·1 of the body weight.

Of the indirect methods, the carbon monoxide method as used by Haldane and Smith,[26] Douglas,[27] Boycott and Douglas,[28] Salvasen[29] and others, and the dye method introduced by Keith, Rowntree and Geraghty[30] are best known.

Using the carbon monoxide method, Douglas[27] found the blood volume of doe rabbits to be 1/18·8 of the body weight and in buck rabbits 1/20·6 of the body weight. Boycott and Douglas[28] found the average blood volume of twenty-two rabbits to be 1/18·6 of the body weight. With the same method Salvasen found the blood volume of male rabbits to be 1/20·2 body weight and 1/19·9 body weight in female rabbits.

As the technique of the carbon monoxide method is more difficult than that of the dye method and as different workers have obtained quite as consistent results with the dye method, it was decided to use the latter method in this study of blood volume in rabbits after lead injections.

Technique.

A 1% solution of vital red in distilled water was made up and sterilized by boiling for ten minutes. Narrow glass tubes of three to four cubic centimetre capacity and graduated in one-hundredths of a cubic centimetre were made from graduated ten cubic centimetre pipettes. A tiny incision was made in the marginal vein of the ear of the rabbit and 2·2 cubic centimetres of blood allowed to flow into a tube containing 0·3 cubic centimetre of 2% potassium oxalate solution. A cork was placed in the tube which was inverted several times.

By means of a one cubic centimetre tuberculin syringe 0·4 cubic centimetre of 1% vital red was injected into the marginal vein of the opposite ear. The rabbit was encouraged to move its limbs and after an interval of two minutes 2·2 cubic centimetres of blood were collected in a similar manner into a second glass tube containing 0·3 cubic centimetre of 2% potassium oxalate solution. The two tubes were then centrifuged for one hour in an electrically driven centrifuge at 3,000 revolutions per minute. The total volume and the plasma volume in each tube were read and the plasma from each tube was pipetted into two other small tubes.

Colorimetric Determination.

A standard solution was prepared from the same dye as was injected into the rabbit. This 1% vital red was diluted one in two hundred with distilled water. A Klett colorimeter was used and the solutions in the two cups were as follows:

(1)	(2)
1 c.cm. 1/200 vital red.	1 c.cm. dye tinged plasma.
1 c.cm. normal saline solution.	2 c.cm. normal saline solution.
1 c.cm. uncoloured plasma.	

The percentage of the dye in (2) as compared with the standard was determined (R).

Calculation:

Let D be the quantity of dye injected.

Let C be the correction for dilution with potassium oxalate.

$$\left(C = \frac{\text{Plasma Volume (in tube)} - 0{\cdot}3}{\text{Plasma Volume (in tube)}}\right)$$

$$\text{Then Plasma Volume} = \frac{200 \times D \times C}{R}$$

$$\text{Blood Volume} = \text{Plasma Volume} \times \frac{\text{Total Volume (in tube)} - 0{\cdot}3}{\text{Plasma Volume (in tube)} - 0{\cdot}3}$$

Red Cell Volume = Blood Volume − Plasma Volume.

Blood volume determinations were made at first on a series of normal rabbits and then on a series of lead poisoned rabbits. The blood volume deter-

minations on the series of normal rabbits are shown in Table II, which also shows the relationship of blood volume to body weight and body surface respectively.

TABLE II.

Rabbit.	Date.	Weight in Grammes.	Plasma Volume in Cubic Centimetres.	Blood Volume in Cubic Centimetres.	Blood Volume in Cubic Centimetres per 100 Grammes Bodyweight.	$\frac{W^{\frac{2}{3}}}{B}$
1	12/2/29	1,050	47	60	5·7	1·72
1	5/2/29	1,085	46	64	5·9	1·65
1	6/2/29	1,088	49	68	6·2	1·55
3	28/2/29	1,100	44	76	6·9	1·40
3	30/1/29	1,170	48	79	6·8	1·40
3	1/2/29	1,195	51	79	6·6	1·43
7	31/1/29	1,266	49	88	6·9	1·33
8	8/2/29	1,288	63	93	7·2	1·27
8	11/2/29	1,290	63	94	7·2	1·26
9	2/3/29	1,350	62	94	7·0	1·30
2	26/1/29	1,360	63	101	7·5	1·22
7	14/12/28	1,368	52	88	6·4	1·40
2	23/1/29	1,380	63	104	7·5	1·10
9	15/2/29	1,410	63	96	6·8	1·31
6	13/12/28	1,810	62	104	5·8	1·42
					Average 6·7	Average 1·38

According to Dreyer and Ray[33] the blood volume of normal healthy rabbits is a function of body surface, not body weight. In their series of rabbits, ranging in weight from 670 to 3,250 grammes, the blood volume expressed as a percentage of body weight diminishes with increasing weight, but expressed as a function of body surface the ratio between blood volume and surface area remains nearly constant.

According to Meeh the surface of an animal equals $K \times W^{\frac{2}{3}}$, where K is a constant for the particular animal and W equals body weight. Dreyer and Ray have expressed the relationship of blood volume to body surface in the formula $\frac{W^{\frac{2}{3}}}{B} = K$, where W = body weight expressed in grammes, B = blood volume expressed in cubic centimetres and K = a constant for the particular animal.

In the results presented in Table II the range of the weight of the rabbits is not nearly so extensive as in Dreyer and Ray's series and with increasing body weight there is no apparent diminution in blood volume expressed as a percentage of body weight. The average percentage of blood volume in terms of body weight is 6·7%, the average deviation from this mean figure is 6·9% and the greatest deviations are +12% and −15%. The average value for K in the formula $K = \frac{W^{\frac{2}{3}}}{B}$ of Dreyer and Ray is 1·38 and the average deviation from this figure is 8·3%. The greatest deviations are +24% and −20%.

Thus it is evident that in this particular series of rabbits, using the dye technique, the relationship of blood volume to body weight is more constant than its relation to body surface.

In Table III are recorded the results in repeated blood volume determinations in the same rabbits after intervals of two to four days. In the four cases the results are fairly consistent. The average blood volume, expressed as a ratio of body weight, is 1/14·7. Using the carbon monoxide method, Boycott and Douglas[28] found the average blood volume of twenty-two rabbits to be 1/18·6 of the body weight. The dye method usually seems to give higher values for blood volume than the carbon monoxide method. Thus Keith, Rowntree and Geraghty[30] found the blood volume of man to be 1/11·4 body weight, while Haldane and Smith,[26] using the carbon monoxide method, found the average blood volume of man to be 1/20·5 body weight. Hooper, Smith and Whipple,[31] with the dye method, found the blood volume of dogs to be 1/9·9 body weight; while Grehard and Quinquard.[32] with the carbon monoxide method, found the blood volume of dogs to be 1/12·1 body weight. In these lead experiments the accurate absolute blood volume was not of such significance as the relative changes in total blood volume and in plasma and corpuscular volumes following lead injections. It was considered that the above results over the fifteen determinations were consistent enough to justify a study of the effect of colloidal lead on blood volume using the dye method.

TABLE III.

Repeated Blood Volume Determinations on Normal Rabbits after Intervals of Two to Four Days.

Rabbit.	Date.	Weight in Grammes.	Plasma Volume in Cubic Centimetres.	Blood Volume in Cubic Centimetres.
II	23/1/29	1,370	63	104
	26/1/29	1,350	63	101
III	30/1/29	1,160	48	79
	1/2/29	1,190	51	79
VIII	8/2/29	1,288	59	93
	11/2/29	1,290	63	94
IX	15/2/29	1,410	62	96
	19/2/29	1,245	60	99

The intravenous injection of colloidal lead causes a certain amount of hæmolysis which interferes with the colorimetric determination. The hæmolysis as indicated by spectroscopic examination has practically disappeared on the second day and has never been detected on the third day after a lead injection. Blood volume determinations were made on the rabbits just before the colloidal lead was injected, and again three days after the lead injection. The dose of lead which was approximately the same for all the rabbits, was 28 milligrammes per kilogram body weight.

The individual results in the eight rabbits are set out in Table IV and the average figures are presented in Table V. The average plasma volume is practically the same three days after the lead injection as it was before, but there is a very marked decrease in the average corpuscular volume. The individual figures show a variation in plasma

TABLE IV.

Rabbit.	Time Relative to Lead Injection.	Weight in Grammes.	Hæmoglobin Percentage (Sahli).	Red Blood Corpuscles in Millions per Cubic Millimetre.	Total Plasma Volume in Cubic Centimetres.	Total Corpuscular Volume in Cubic Centimetres.	Total Blood Volume in Cubic Centimetres.
2	Immediately before	1,430	60	4·50	67	38	105
2	Three days after	1,428	39	3·20	66	19	85
3	Immediately before	1,162	67	4·40	49	26	70
3	Three days after	1,136	49	3·10	43	13	56
7	Immediately before	1,208	72	5·00	53	29	82
7	Three days after	1,195	50	3·80	56	16	72
9	Immediately before	1,213	63	5·06	49	28	77
9	Three days after	1,226	43	3·30	58	14	72
11	Immediately before	1,297	75	6·20	54	34	88
11	Three days after	1,202	60	4·80	50	23	73
12	Immediately before	1,214	79	6·60	46	35	81
12	Three days after	1,148	54	4·10	57	21	78
13	Immediately before	1,416	75	4·90	51	35	86
13	Three days after	1,261	48	3·20	49	15	64
16	Immediately before	1,287	65	4·26	61	34	95
16	Three days after	1,243	52	3·48	59	22	81

volume after lead. It is probable that experimental error can account largely for the individual changes in plasma volume. The fall in corpuscular volume is particularly striking and compared with this fall the plasma volume remains almost constant.

There is a discrepancy in the fall in red cell count as compared with the fall in corpuscular volume. Thus there is a 29% fall in red cell count, while there is a 43% fall in corpuscular volume. If the fall in red cell count be corrected for the actual shrinkage in total blood volume, the percentage fall would be 39%. The remaining difference of 4% is possibly due to the fact that average diameter of the cells is less than normal and so a given number of cells occupies a smaller volume.

CHANGES IN THE WHITE BLOOD CELLS AND PLATELETS FOLLOWING AN INJECTION OF COLLOIDAL LEAD.

In the following experiments leucocyte and platelet counts were made at regular intervals after an injection of colloidal lead and changes in the total counts and in the differential white cell count were observed over a period of seventeen days.

Technique for Blood Counts.

Leucocytes.

The diluting fluid was 1% acetic acid in distilled water. Dilutions (1 to 20) were made with Thoma-Zeiss pipettes and the count was made in an all glass Thoma-Zeiss counting chamber. The same pipettes were used in all the experiments and the author made all the counts. The differential counts were made from films stained by the Giemsa method and 300 to 400 cells were counted.

Platelets.

The platelets were counted by the indirect method described by W. Howell Evans.[34] The anticoagulant solution used was 2% sodium citrate in 0·29% sodium chloride. This solution was kept sterile and sufficient cresyl blue was added to make a 0·3% solution of the dye. A paraffin cell and a paraffined pipette were used and one to two drops of blood were thoroughly mixed with about five cubic centimetres of solution for five minutes. A drop of the suspension was placed in a Thoma-Zeiss counting chamber and 2,000 red cells and a corresponding number of platelets were counted. The absolute platelet count was then determined from the red cell count.

Blood Samples.

Blood samples were taken from the dilated marginal vein of the ear. A. F. Bernard-Shaw[35] has shown that the leucocyte count is always greater during constriction than dilatation, the difference being sometimes 300% to 600% and the counts are much more constant during vaso-dilation.

TABLE V.

Average for Eight Rabbits.

Time Relative to Lead Injection (28 milligrammes per kilogram).	Weight in Grammes.	Hæmoglobin Percentage (Sahli).	Red Blood Corpuscles in Millions per Cubic Millimetre.	Plasma Volume in Cubic Centimetres.	Corpuscular Volume in Cubic Centimetres.	Blood Volume in Cubic Centimetres.
Immediately before	1,278	69	5·10	52	32	84
Three days after	1,229	49	3·62	54	18	72

Results.

Blood counts from thirty-four apparently normal rabbits showed that the range of variation in the total leucocyte count was not very pronounced, but in the differential counts quite an appreciable difference between individual counts was evident. To render this individual difference as negligible as possible a large number of observations were made at frequent intervals. Blood counts were obtained from at least five rabbits at intervals of four hours, eight hours, 12 hours, 24 hours, 48 hours, 72 hours, seven days, 10 days, 14 days, 17 days after an injection of colloidal lead and practically all the counts were made in the latter part of the afternoon. This time factor is important, as A. F. Bernard Shaw[36] has shown that in man there is a diurnal variation in the number of leucocytes. He found that the leucocytes exhibit two tides—a day tide and a night tide—and the day tide reaches its flood in the afternoon, while during the morning the night tide ebbs away. Thus the leucocyte count is always raised in the afternoon.

The dose of lead given varied in individual cases from 20 milligrammes to 35 milligrammes per kilogram body weight. Full details of the fifty-three blood examinations are not shown, but the average count for each group of five or six rabbits at the different time intervals is presented in Table VI. The differential count is given in absolute numbers, not in percentages. The normal count is the average of the blood examinations made on thirty-four normal rabbits. These results are represented graphically in Chart III.

Immediately after the injection of lead there was a definite leucocytosis. In two days there was an increase from 5,000 to 19,400 white blood cells per cubic millimetre. This immediate reaction was due almost solely to a rise in the number of neutrophile polymorphonuclear leucocytes. These cells were most numerous eight hours after the injection and subsequently their number in the peripheral blood was gradually diminished. At this period (eight hours after the lead injection) when the neutrophilia is at its height, many damaged polymorphonuclear leucocytes were observed. Figure II is a drawing of several of these cells seen in Giemsa stained films.

The damaged cells were smaller in size than the normal neutrophile polymorphonuclear leucocytes and exhibited marked changes in the morphology of nucleus and cytoplasm. The nucleus was pyknotic and fragmented. There was no chromatin structure visible and the characteristic lobular arrangement was grossly distorted. The cytoplasm was acidophilic and contained eosinophilic granules which were fewer, less distinct and less evenly distributed than in normal cells. In one rabbit 6% of the neutrophile polymorphonuclear leucocytes showed these degenerative changes.

The increase in metamyelocytes corresponded with the increase in neutrophile polymorphonuclear cells and these immature cells were back to their normal level in the peripheral blood three days after lead injection. The relatively high count of metamyelocytes given for the ten day period after injection was due to a terminal 20% count in rabbit 41A taken just before the animal died.

The basophile polymorphonuclear leucocytes also rose and fell with the neutrophile polymorphonuclear cells, but the eosinophile polymorphonuclear cells were diminished in number while the neutrophilia was at its height, and then when the neutrophile cells fell in number, the eosinophile cells showed a temporary slight increase.

TABLE VI.

Time of Count.	Red Cells in Millions.	White Cells per Cubic Millimetre.	Platelets per Cubic Millimetre.	Polymorphonuclear Neutrophile Cells.	Polymorphonuclear Eosinophile Cells.	Polymorphonuclear Basophile Cells.	Lymphocytes.	Large Mononuclear Cells.	Metamyelocytes.
Normal count before lead injection ..	5·20	5,000	245,000	2,615	30	35	1,840	375	105
4 hours after lead injection ..	4·87	12,800	254,000	8,691	25	13	2,714	589	768
8 hours after lead injection ..	4·30	13,000	383,000	9,047	11	130	2,665	550	617
12 hours after lead injection ..	4·38	14,600	593,000	8,347	14	160	4,064	964	1,022 Myelocytes. 29
24 hours after lead injection ..	4·32	15,200	358,000	8,618	9	46	4,575	1,408	544
2 days after lead injection ..	3·97	19,800	400,000	7,347	48	16	9,691	2,045	655
3 days after lead injection ..	3·84	12,000	323,000	4,629	81	81	6,044	964	201
7 days after lead injection ..	4·23	7,200	251,000	2,678	58	14	3,521	828	100
10 days after lead injection ..	4·14	7,300	312,000	2,905	44	22	3,125	716	489
14 days after lead injection ..	4·10	6,900	283,000	2,781	7	48	3,574	306	186
17 days after lead injection ..	4·52	9,300	324,000	2,920	19	46	5,524	521	270

The lymphocytes exhibited a more gradual and a greater increase in number after the lead injection than did the polymorphonuclear leucocytes. The maximum rise in lymphocytes was reached two days after lead injection, when these cells had increased in absolute number from 1,840 to 9,200; subsequently the count fell, but throughout the period of observation the lymphocytes were more numerous than the polymorphonuclear leucocytes. The large mononuclear cells increased and diminished in number correspondingly with the lymphocytes. The classification of mononuclear cells adopted includes only small lymphocytes as lymphocytes and all large mononucleated cells, whether showing indented nuclei with coarse chromatin strands or not, as large mononuclear cells. The characteristics of Naegeli's monocyte are not available for differentiation, as for instance the cytoplasm of all large mononuclear cells of the rabbit is non-granular, so to simplify the differential count all large mononuclear cells have been included in one group.

The platelets showed a marked and rapid increase in number after the lead injection and the maximum was reached in twelve hours. The rise lags somewhat behind the rise in neutrophile polymorphonuclear cells, for these cells had almost reached their maximum number before the platelets had commenced to increase in number and at twelve hours, when the platelets were at a maximum, the neutrophile cells were diminishing in number. After twelve hours the platelets fell rapidly and in twenty-four hours the count was within the normal range of variation.

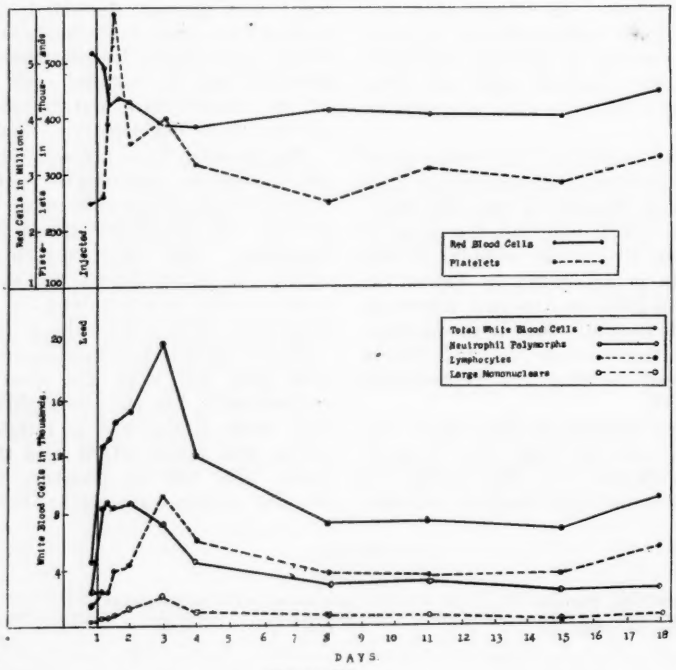

CHART III.

CHANGES IN THE BONE MARROW FOLLOWING AN INJECTION OF COLLOIDAL LEAD.

Sections of bone marrow were taken from the same rabbits as were used in studying the effect of colloidal lead injections on the leucocytes and platelets and the bone marrow was taken from at least three rabbits at the same intervals of time.

Technique.

The rabbits were anæsthetized lethally with chloroform and a small piece of bone marrow was removed from the centre of the shaft of the femur. A complete *post mortem* examination was made to exclude pathological abnormality. The method of preparation and staining of the sections was a slight modification of the technique described by W. Stump.[37] The tissue was fixed in a saturated solution of mercuric chloride in saline at 37° C. to 100 cubic centimetres, of which one cubic centimetre of 1% osmic acid solution was added immediately after introducing the tissue. The specimen bottles were tightly corked and after four to twelve hours' immersion the tissue was transferred to Helly's fluid at 37° C. for twelve hours. The Helly's fluid was made up from neutral formalin. The tissue was washed in neutral distilled water at 37° C. for thirty-six hours and then dehydrated by passing through the alcohols. After immersion for two to four hours in 50% alcohol the strength was made up to 80% by adding absolute alcohol drop by drop. The tissue was kept in freshly prepared 80% alcohol for twelve hours and then the strength made up to 95% by adding absolute alcohol drop by drop. The tissue was then transferred to absolute alcohol which had been dehydrated with quicklime, for two changes over four hours. Cedarwood oil was used in four changes over seventy-two hours to remove the alcohol. The tissue was passed through five baths of paraffin at 54° C. over a period of six hours. Sections were cut and mounted on wet clean slides and fixed to the slide by careful pressure and dried at 52° C. for five minutes. After removing the paraffin with xylol and then passing back through the alcohols from absolute to 50%, the mercuric chloride was removed with Lugol's solution diluted one in six with distilled water for three to four minutes. The iodine was then removed with 50% alcohol for three to four minutes.

The sections were stained with 10% eosin at 37° C. for ten to twenty minutes, then with polychrome methylene blue (Grübler's) for thirty to sixty minutes. After washing, the sections were differentiated by passing through alcohols from 50% to 95% (the latter containing 3% colophonium), then briefly dehydrated with absolute alcohol, cleared

with xylol and mounted in neutral Canada balsam in xylol.

Microscopical Observations.

Normal Bone Marrow: Rabbits A, B and C.

Bone marrow was examined from three rabbits, the blood examinations of which were normal and no pathological abnormalities were revealed at *post mortem* examination. Figure III shows a low power field of a section taken from rabbit B and demonstrates fat spaces with hæmatopoietic tissue in the interstices.

Megalokaryocytes were counted and in 50 high power fields (equivalent to an area of 3·5 square millimetres) 87, 93 and 84 of these cells were observed in the three sections respectively.

Bone Marrow Four Hours after Lead Injection: Rabbits 5A, 13A, 14A.

Magnification × *80.*—In the three sections the most outstanding feature under the low power magnification was the intense congestion. Fat cells were present in sections 5A and 14A as in normal marrow, but in section 13A no fat spaces were visible and the hæmatopoietic cells appear in groups on a very faintly stained background. Figure IV shows the congestion of capillaries and the absence of fat spaces.

In a part of section 14A the blood forming cells had largely disappeared and a network of fat cells supporting relatively few cells remained.

Magnification × *400.*—The background in section 13A was a faintly stained reticular syncytium with a fibrillated appearance and occasional pale oval nuclei. Myelocytes, normoblasts and more immature cells with vesicular nuclei exhibiting a loose chromatin structure with nucleoli and clear basophilic cytoplasm were distributed throughout the section without evidence of any structural arrangement. In section 14A normoblasts were numerous and many pyknotic nuclei were seen. In this section 82 megalokaryocytes were counted in 50 high power fields (equivalent to an area of 3·5 square millimetres), and many of these cells were seen showing pyknotic changes in the nuclei (Figure V). Section 5A showed a great number of myelocytes. No abnormality in these cells could be detected and mitotic figures are numerous.

Magnification × *900.*—In section 13A a few polymorphonuclear leucocytes were seen showing fragmented pyknotic nuclei and in section 14A many pyknotic normoblast nuclei and occasional megalokaryocytes with pyknotic nuclei were seen, but otherwise no evidence of gross cellular damage could be found. The reticular syncytium in section 13A had a finely granular fibrillated structure and showed pale oval nuclei and occasional vacuoles, probably fat globules.

Bone Marrow Eight Hours after Lead Injection: Rabbits 12A, 16A *and* 21A.

Magnification × *80.*—All three sections had an appearance suggesting the effect of an injury. There was congestion, no fat spaces and a disorderly arrangement of cells. Section 16A showed intense congestion and a general extravasation of red blood corpuscles, many of which had apparently disintegrated and the nuclei of many megalokaryocytes were pyknotic (Figure VI). Sections 12A and 21A showed similar changes in a less marked degree.

Magnification × *400.*—In section 16A the supporting reticulum appeared as an irregular branching fibrillar syncytium with pale oval nuclei and occasional vacuoles. This reticulum had a distorted appearance and scattered over it were many disintegrating and normal red cells and blood forming cells appeared singly and in small groups. There were many pyknotic normoblast nuclei and nuclear fragments, while myelocytes and their immediate progenitors and successors were apparently quite normal. In section 21A many macrophages were seen containing yellow pigmented granules (Figure VII), which with the ferricyanide and hydrochloric acid test for iron gave a positive reaction. These macrophages also contained nuclear fragments which probably originated from normoblasts as there were many pyknotic normoblast nuclei in this section and the nuclei of other hæmatopoietic cells were apparently normal. Section 12A had a similar appearance, although the reticulum was not so distorted as in section 16A and there was less pigment than in section 21A. In this section 172 megalokaryocytes were counted in fifty high power fields.

Magnification × *900.*—The pyknotic nuclei of normoblasts and occasional polymorphonuclear leucocytes were observed, but the nuclei of more immature cells appeared to be uninjured by the lead and mitotic figures were quite numerous (Figure VIII). In the three sections the cytoplasm of the reticulum was seen to be finely granular and fibrillar with occasional large vacuoles (Figure IX).

Bone Marrow Twelve Hours after Lead Injection: Rabbits 10A, 18A *and* 29A.

Magnification × *80.*—Sections 10A and 18A were seen to be packed with cells which, even at this magnification, could be recognized as myelocytes (Figure X). Section 29A showed intense congestion and resembled sections taken eight hours after lead injection.

Magnification × *400.*—In the three sections myelocytes were actively proliferating and section 10A was packed with myelocytes, premyelocytes and metamyelocytes. There were also many megalokaryocytes present and in section 10A 159 of these cells were counted in 50 high power fields. The nuclei of megalokaryocytes showed occasional pyknotic changes, but also many mitotic figures were seen (Figure XI). In section 29A the cells were in haphazard arrangement and there was much congestion.

Magnification × *900.*—In section 29A with oil immersion objective the reticulum was seen to be composed of cells resembling embryonic fat cells. These cells have a vesicular pale oval nucleus with abundant branching cytoplasm packed with small vacuoles (Figure XII). To determine if these vacuoles represented fat globules, a smear of bone marrow was taken from rabbit D eighteen hours after lead injection and stained with Sudan III and Nile blue sulphate. The cytoplasm stained pink with Nile blue sulphate and red with Sudan III and thus it is evident that the vacuoles in the cytoplasm represent fat globules. In section 10A there were so many myeloid cells that it was impossible to observe the structure of the reticulum. In section 18A the cells of the reticulum were seen to have oval vesicular nuclei with abundant branching cytoplasm which was stained faintly and only occasional cells could be recognized containing small fat spaces.

Bone Marrow Twenty-four Hours after Lead Injection: Rabbits 8A *and* 17A.

Magnification × *80.*—Both sections showed a hyperplasia of cells with myelocytes easily predominating in section 8A (Figure XIII), and while section 17A was packed with myelocytes, there were also an increased number of normoblasts. The vessels, particularly the capillary sinusoids, were engorged and there was a more definite structural arrangement than in previous sections. Masses of granular cells and normoblasts seemed to be proliferating apace.

Magnification × *400.*—Both sections were crowded with hæmatopoietic cells. In section 8A myelocytes predominate, while in section 17A there were masses of normoblasts mingled with the myelocytes. Megalokaryocytes were very numerous in both sections and in section 17A 162 megalokaryocytes were counted in 50 high power fields.

Magnification × *900.*—In section 17A the supporting tissue consists of a branching reticulum of fat cells with pale oval vesicular nuclei and relatively large fat globules. There were many mitotic figures in myelocytes and normoblasts.

Bone Marrow Two Days after Lead Injection: Rabbits 19A, 20A *and* 45A.

Magnification × *80.*—Sections from rabbits 19A and 45A showed a very cellular bone marrow with no fat spaces visible (Figure XIV). Granular cells predominate in section 19A, while in section 45A there is also an increased number of normoblasts. Rabbit 20A died between two and three days after an injection of lead, and bone marrow was taken for section several hours after death. In this section there was very marked dilatation and engorge-

ment of the capillary sinusoids and hæmatopoietic cells were scattered and relatively infrequent (Figure XV). There was slight engorgement of capillaries in section 19A, but no obvious engorgement in section 45A.

Magnification × *400.*—The bone marrow in sections 19A and 45A was packed with hæmatopoietic cells, the myelocytes easily predominating in number over the other cells. Normoblasts in section 45A were also in evidence in groups and lines of cells as well as singly mixed up with the granular cells. In section 19A there were a large number of metamyelocytes and polymorphonuclear leucocytes and 85 megalokaryocytes were counted in 50 high power fields. The bone marrow in section 20A was relatively depleted in cells and there were no groups of actively proliferating myelocytes or normoblasts. The cells were quite discrete and separated from one another. The dilated sinusoids were much in evidence and except for an occasional endothelial cell nucleus, no definite lining membrane could be detected.

Magnification × *900.*—The reticulum in sections 19A and 45A was obscured by the conglomeration of blood forming cells and although the fixation and staining were not so definite as in section 29A, yet the "embryonic" type of fat cell could be recognized. In section 20A the reticulum had a granular appearance and was very faintly stained, the nuclei were pale, oval and vesicular and the cytoplasm abundant and branching and an occasional large fat space was observed. The blood forming cells were exceedingly numerous in sections 19A and 45A with myelocytes predominating.

Bone Marrow Three Days after Lead Injection: Rabbits 6A, 23A *and* 46A.

Magnification × *80.*—All sections showed a marked hyperplasia of hæmatopoietic cells, particularly in section 6A, in which the granular cells were packed closely together throughout the section, while in sections 23A and 46A there were fewer granular cells and an increased number of normoblasts (Figure XVI). Section 6A showed much yellow pigment which was quite visible at this magnification.

Magnification × *400.*—In two of the three sections, namely, sections 23A and 46A, normoblasts were predominant. These cells showed a tendency to group formation composed of more immature cells with large nuclei showing a more open chromatin structure. Many mitotic figures were observed. Some of the nuclei showed dumbbell, clover leaf and such like bizarre shapes and many pyknotic nuclei were seen. Sections 6A presented an appearance resembling that of sections taken at earlier periods after lead injection. The section was packed with myelocytes and showed relatively few normoblasts. An interesting feature of this section was the excessive amount of yellow iron-containing pigment granules contained in macrophages and also apparently free in tissue spaces. Section 46A also showed many myelocytes and normoblasts were fewer in number than in section 23A; 96 megalokaryocytes were counted in 50 high power fields.

Magnification × *900.*—The characteristic feature of section 23A was masses of normoblasts with many mitotic figures. Myelocytes in sections 6A and 46A were very numerous and showed many mitotic figures. A reticular framework composed largely of the "embryonic" type of fat cell was observed in sections 23A and 46A, but section 6A was so crowded with myelocytes that the reticulum was completely obscured.

Bone Marrow Seven Days after Lead Injection: Rabbits 2A, 9A, 22A *and* 25A.

Magnification × *80.*—Sections 2A, 9A and 22A showed a reappearance of fat spaces and in these sections myelocytes were relatively infrequent and normoblasts predominated (Figure XVII). In section 25A there were no apparent fat spaces and the section showed more granular cells. All four sections showed congestion of capillary sinusoids, it being particularly noticeable in section 22A.

Magnification × *400.*—In section 22A spaces between hæmatopoietic cells were occupied by a branching reticulum with pale oval nuclei and enclosing fat spaces of varying size. In sections 2A and 9A fat cells were seen to be of normal size with one large fat space surrounded by a thin rim of cytoplasm and nucleus. In sections 2A, 9A and 22A there was much congestion of capillary blood vessels and active proliferation of normoblasts with less active hyperplasia of myelocytes. Section 25A was crowded with blood forming cells with no fat spaces visible and myelocytes predominating. Sixty-seven megalokaryocytes were counted in 50 high power fields in section 22A.

Magnification × *900.*—The characteristic features in section 22A were masses of young normoblasts with many mitotic figures, an open fibrillar reticulum with occasional pale oval nuclei and larger fat spaces than in previous sections. Macrophages containing iron reacting yellow pigment, myelocytes and occasional more immature cells, probably myeloblasts, were observed. Section 25A was packed with myelocytes, metamyelocytes, normoblasts and relatively few myelocytes. The normoblasts were distributed fairly evenly throughout the section and showed a marked tendency for an arrangement into masses. There was a marked congestion of capillary blood vessels in section 42A, but such congestion was not obvious in section 43A.

Bone Marrow Ten Days after Lead Injection: Rabbits 42A *and* 43A.

Magnification × *80.*—Both sections showed hyperplasia of hæmatopoietic cells with appearance of occasional fat spaces and marked congestion. Whereas section 42A showed many myelocytes as well as normoblasts, the bone marrow in section 43A was apparently given over almost solely to the multiplication of normoblasts and the manufacture of red blood corpuscles. These normoblasts were most numerous towards the periphery of the bone marrow.

Magnification × *400.*—Section 42A showed a general hyperplasia of hæmatopoietic cells with normoblasts and myelocytes proliferating at approximately equal rates, while megalocaryocytes appeared to be quite numerous—101 of these cells were counted in 50 high power fields. Section 43A showed an enormous number of normoblasts and relatively few myelocytes. The normoblasts were distributed fairly evenly throughout the section and showed a marked tendency for an arrangement into masses. There was a marked congestion of capillary blood vessels in section 42A, but such congestion was not obvious in section 43A.

Magnification × *900.*—Section 42A showed all types of developing blood cells; normoblasts and myelocytes were most numerous, but there were also many myeloblasts and macrophages which contained a lesser amount of yellow pigment than in previous sections. Section 43A showed a large preponderance of normoblasts, many of which manifested the more open chromatin network characteristic of the more immature cells. Many mitotic figures were also seen (Figure XVIII). Occasional fat cells of the "embryonic" type were observed and also cells with larger fat spaces and occasional fully developed fat cells with nucleus and cytoplasm compressed into a thin rim enclosing a large fat space.

Bone Marrow Fourteen Days after Lead Injection: Rabbits 37A, 38A *and* 39A.

Magnification × *80.*—The three sections were very cellular, with only occasional fat spaces visible. Section 38A resembled in appearance the so-called gelatinous degeneration of bone marrow. Between the groups and columns of normoblasts there appeared a structureless, very faintly stained supporting tissue. Sections 37A and 39A showed a general hyperplasia of hæmatopoietic cells.

Magnification × *400.*—Sections 37A and 39A showed a general hyperplasia of all types of bone marrow cells on a faintly stained reticular ground substance exhibiting oval nuclei and occasional fat spaces. Section 38A showed a similar histological structure towards the centre of the pencil of marrow, but towards the periphery there was evidence of very marked proliferation of normoblasts which were arranged in small clumps. In section 39A sixty-seven megalokaryocytes were counted in 50 high power fields.

Magnification × *900.*—In all three sections the reticulum showed both the "embryonic" type of fat cell and the

more fully developed fat cells, the latter being more numerous, but neither were conspicuous owing to the proliferation of blood forming cells. In section 38A the reticulum was more obvious in areas described as resembling gelatinous degeneration. The cytoplasm was faintly stained with eosin and exhibited very fine eosinophilic granules and there was a very loose branching network of cytoplasmic processes. The nuclei were pale and oval in shape and relatively infrequent. In the groups of normoblasts mitotic figures were observed quite frequently (Figure XIX).

Bone Marrow Seventeen Days after Lead Injection: Rabbits 31A, 32A *and* 34A.

Magnification × *80.*—Section 32A showed fat spaces to be as numerous as in normal marrow and the section had a normal appearance (Figure XX), but sections 31A and 34A, although less cellular than sections taken at earlier periods after lead injection, show the same faintly stained ground substance with only occasional fat spaces as has been observed in previous sections.

Magnification × *400.*—In certain areas of section 32A hæmatopoiesis was at the normal level as indicated by closely packed fat spaces, but in other areas there was still evidence of increased blood cell formation, more particularly involving normoblasts, and fat spaces were to a certain extent obscured. Sections 31A and 34A showed evidence of increased formation of blood cells, but the bone marrow was much less cellular than in previous sections. In section 32A there were 104 megalokaryocytes in 50 high power fields.

Magnification × *900.*—The fat spaces in sections 31A and 34A were relatively large and only a very occasional "embryonic" type of fat cell could be seen. In section 32A the fat cells were all fully developed with a single dilated fat space and thin flattened nucleus. Groups of myelocytes and normoblasts exhibited active multiplication as evidenced by many mitotic figures.

Summary of Microscopical Observations.

The first phase after an injection of lead was characterized by the disappearance of fat spaces, intense congestion and a disorderly arrangement of cells. These findings were particularly in evidence four hours and eight hours after injection. Cell damage was indicated by pyknotic changes in the nuclei of polymorphonuclear leucocytes, megalokaryocytes and normoblasts and by the presence of an excessive amount of iron containing yellow pigment. The more immature myelocytes and myeloblasts appeared to be undamaged by the lead and mitotic figures in these cells were quite numerous. Eight hours after lead injection there was a greatly increased number of megalokaryocytes—172 of these cells were counted in an area of 3·5 square millimetres, as compared with the normal count of 88. The reticulum showed a fibrillar structure rather poorly stained, with small spherical spaces and pale oval vesicular nuclei.

The next phase presented many interesting features. Twelve hours after lead injection there was a marked preponderance of myelocytes—the bone marrow from rabbit 10A was absolutely packed with myelocytes. Subsequently, at twenty-four hours and two days after lead injection, though myelocytes still predominated, normoblasts commenced to appear in increasing numbers. Megalokaryocytes were still numerous; at twelve hours there were 159 and at twenty-four hours there were 162 of these cells in 3·5 square millimetres, but later sections showed a normal number of these cells. An interesting phenomenon was the presence of cells with central pale oval nuclei exhibiting a fine scanty chromatin network and abundant branching cytoplasm packed with small vacuoles. Fresh smears stained with Nile blue sulphate and Sudan III demonstrated the cytoplasm to be fat containing. The resemblance of these cells to embryonic fat cells was striking. The reticulum in section 29A was composed almost solely of this "embryonic" type of fat cell and these cells were also in evidence in sections taken at later periods after lead injection.

Sections taken three days after lead injection represented a transitional stage. In two of the three sections examined myelocytes predominated, but in one section normoblasts were in excess and subsequently in all sections normoblasts predominated in number over myelocytes. The "embryonic" type of fat cell was in evidence except where the marrow was so cellular as to obscure the reticulum. Much yellow iron reacting pigment was present in macrophages, which also contained nuclear fragments.

Sections taken seven days, ten days and fourteen days after lead injection showed a hyperplasia of hæmatopoietic tissue, particularly involving normoblasts. All types of fat cells were represented at this period—the "embryonic" type of cell with numerous small fat spaces, cells at a later stage in development showing fewer and larger fat spaces and, finally, fully developed fat cells with a single large fat space and a thin rim of cytoplasm and flattened nucleus. In all sections macrophages were observed containing yellow iron reacting pigment and cell *débris*.

The last phase was indicated in sections taken seventeen days after lead injection when a return to the normal level of hæmatopoiesis was evident, particularly in section 32A. In this section the bone marrow had quite a normal appearance, but the other two sections still showed evidence of increased hæmatopoiesis, particularly involving normoblasts, and fat spaces were not so large or so numerous as in section 32A.

Changes in Spleen and Mesenteric Lymph Glands.

Spleen sections were taken at frequent intervals, ranging from twelve hours to twenty-three days after injection of lead, from thirteen rabbits. Mesenteric gland sections were obtained from six rabbits at intervals up to ten days after lead injection. A similar technique was used in fixing and staining sections from lymph glands as was used for the bone marrow sections. Sections of spleen were fixed in formalin and stained in the routine way with hæmalum and eosin.

Microscopical Observations.

Spleen from Rabbit 29A *which was Killed Twelve Hours after Lead Injection.*

Magnification × *80.*—The pulp showed much congestion and Malpighian bodies showed a large amount of lymphoid tissue with occasional germinal centres.

Magnification × *400.*—Much cell *débris* and many fragmented pyknotic nuclei were observed, particularly in the pulp, contained in macrophages and also apparently free in tissue spaces.

Spleen from Rabbit 15 *which Died about Twelve Hours after Lead Injection.*

Magnification × *80.*—Generalized fibrosis of the pulp was evident with all defined Malpighian bodies showing scanty lymphoid tissue and no germinal centres.

Magnification × *400.*—The tissue of the pulp appeared to be composed of a fibrillar reticular syncytium, with elongated vesicular nuclei. Lymphocytes were scanty and many macrophages were present containing brown pigment which gave a positive reaction to the ferricyanide and hydrochloric acid test for iron.

Spleen from Rabbit B1 *Killed Twenty-four Hours after Lead Injection.*

Magnification × *80.*—Marked congestion of pulp was observed with obvious Malpighian bodies containing much lymphoid tissue and many germinal centres.

Magnification × *400.*—Congestion of venous sinuses was present with much brown iron reacting pigment contained in macrophages (Figure XXI). Malpighian bodies showed germinal centres with the usual group of large cells with vesicular nuclei surrounded by an abundant number of small lymphocytes.

Spleen from Rabbit 45A *Killed Two Days after Lead Injection.*

Magnification × *80.*—The pulp was congested with well marked Malpighian bodies containing abundant lymphoid tissue with germinal centres.

Magnification × *400.*—Macrophages in pulp contained cell *débris*, but very little pigment was seen. Well defined germinal centres were present in the lymphoid tissue of Malpighian bodies.

Spleen from Rabbit 10 *which Died Two Days after Lead Injection.*

Magnification × *80.*—Pulp showed congestion and an appearance simulating a general fibrosis. Lymphoid tissue, except for an occasional atrophic Malpighian body, was practically absent from the section and no germinal centres were seen. A small hæmorrhagic infarct was observed.

Magnification × *400.*—The pulp was composed largely of cells with oval deeply staining nuclei in a fibrillar reticular syncytium. In certain areas there was evidence of marked necrosis of the pulp tissue as indicated by pyknotic fragmented nuclei on a structureless eosin stained background. Such an area was present involving what was previously a Malpighian body situated at the apex of the infarction. Small arterioles, as a rule, were not surrounded by a cuff of lymphoid tissue and Malpighian bodies, which could be recognized as such, showed very few lymphocytes.

Spleen from Rabbit 20 *which Died Two Days after Lead Injection.*

Magnification × *80.*—Thickened capsule and well marked trabeculæ with much congestion of pulp and an appearance resembling that described in section X were observed and lymphoid tissue was practically absent.

Magnification × *400.*—The pulp showed the same reticular structure as in section from rabbit 10 and no lymphoid tissue and no Malpighian bodies could be recognized containing a definite cuff of lymphocytes.

Spleen from Rabbit 14 *which Died Two and a Half Days after Lead Injection.*

Magnification × *80.*—Much congestion, many areas of necrosis and great depletion of lymphoid tissue were the outstanding features observed.

Magnification × *400.*—An enormous number of pyknotic fragmented nuclei with few normal cells and very few lymphocytes were observed. Brown pigment in small granules was scattered throughout the section, but none was seen located in macrophages.

Spleen from Rabbit 46A *Killed Three Days after Lead Injection.*

Magnification × *80.*—Congestion of pulp, Malpighian bodies well defined with abundant lymphoid tissue and occasional germinal centres were the outstanding features observed.

Magnification × *400.*—Venous sinuses were packed with red corpuscles and the pulp was relatively very cellular. Cells with oval and round vesicular nuclei and very little cytoplasmic structure could be seen.

Spleen from Rabbit 25A *Killed Seven Days after Lead Injection.*

Magnification × *80.*—The pulp was congested and the Malpighian bodies showed abundant lymphoid tissue and many germinal centres (Figure XXII).

Magnification × *400.*—Many mitotic figures were observed in the large lymphocytes of the Malpighian bodies. The pulp was congested and showed many macrophages containing brownish-yellow iron reacting pigment and cell *débris* and quite a few myelocytes were observed. (Section was fixed and stained by eosin methylene blue method as used for bone marrow.)

Spleen from Rabbit 7 *which Died Eight Days after Lead Injection.*

Magnification × *80.*—Capsule was thickened and the pulp fibrotic with scanty amount of lymphoid tissue and no germinal centres (Figure XXIII).

Magnification × *400.*—The pulp was relatively acellular and was devoid of red blood cells. Pulp cells showed a deeply stained elongated nucleus with faintly stained cytoplasm. Much brown pigment was scattered diffusely throughout the section and also contained in macrophages. Malpighian bodies showed few lymphocytes and no germinal centres.

Spleen from Rabbit 41A *which Died Ten Days after Lead Injection.*

Magnification × *80.*—The capsule was thickened and the pulp was congested. Lymphoid tissue was scanty, with absence of germinal centres.

Magnification × *400.*—A large number of macrophages were present in the pulp containing brown pigment and cell fragments and occasional intact red blood cells. Lymphocytes were infrequent and showed pyknotic nuclei.

Spleen from Rabbit 37A *Killed Fourteen Days after Lead Injection.*

Magnification × *80.*—Increased amount of lymphoid tissue was observed in Malpighian bodies which showed many germinal centres.

Magnification × *400.*—The pulp was congested and was relatively acellular, showing reticulum cells with oval well stained vesicular nuclei, fibrillated cytoplasm and many macrophages. The lymphoid tissue in this section was quite abundant.

Spleen from Rabbit 31 *Killed Seventeen Days after Lead Injection.*

Magnification × *80.*—There was congestion of the pulp and the Malpighian bodies showed a large amount of lymphoid tissue with many germinal centres.

Magnification × *400.*—Germinal centres were frequent and showed many mitotic figures. Endothelial cells and reticular cells in the pulp showed well stained vesicular nuclei. Macrophages were infrequent.

Mesenteric Gland from Rabbit 47 *Killed Twelve Hours after Lead Injection.*

Magnification × *80.*—The cortex of the gland showed abundant lymphoid tissue with many germinal centres. The medulla was apparently normal.

Magnification × *400.*—The nuclei of many lymphocytes appeared to be pyknotic and cell fragments were observed. No mitotic figures could be found.

Mesenteric Gland from Rabbit Killed Eighteen Hours after Lead Injection.

Magnification × *80.*—The gland was packed with lymphocytes and many germinal centres were obvious.

Magnification × *400.*—Cell *débris* and occasional fragmented pyknotic nuclei were observed free in tissue spaces and contained in macrophages. No mitotic figures could be seen.

Mesenteric Gland from Rabbit B1 *Killed Twenty-four Hours after Lead Injection.*

Magnification × *80.*—No obvious abnormality could be seen. Lymphoid tissue was abundant with germinal centres in cortex.

Magnification × *400.*—Many pyknotic nuclei and cell fragments were seen and there were increased numbers of macrophages, particularly in the medullary portion of the gland. Occasional mitotic figures were observed.

Mesenteric Gland from Rabbit 45A *Killed Two Days after Lead Injection.*

Magnification × *80.*—In this section there was an excessive number of very clearly demarcated germinal centres (Figure XXIV).

Magnification × *400.*—Many macrophages containing nuclear fragments and cell *débris* were observed and these cells were particularly obvious in lymphatic sinuses. Germinal centres showed mitotic figures.

Mesenteric Gland from Rabbit 46A *Killed Three Days after Lead Infection.*

Magnification × *80.*—Many germinal centres were present in the lymphatic tissue of the cortex.

Magnification × *400.*—In this section also many macrophages were observed and many contained yellow pigment giving a positive reaction for iron (Figure XXV). Only a very occasional mitotic figure could be seen.

Mesenteric Gland from Rabbit 41A *which Died Ten Days after Lead Injection.*

Magnification × *80.*—Lymphoid tissue relatively scanty and no germinal centres were seen.

Magnification × *400.*—In the cortex there was a reticular syncytium with oval vesicular nuclei and a fibrillated branching cytoplasm. Few lymphocytes were present and no mitotic figures could be found. The medulla was largely depleted of cells, but showed many macrophages.

Summary of Microscopical Observations.

A conception of the changes which have occurred in the tissue of spleen and lymph glands is simplified if the sections be classified into two groups, characterized respectively by a hyperplasia of lymphoid tissue and by an aplasia of lymphoid tissue.

There was a marked hyperplasia of lymphatic tissue with many germinal centres in all the rabbits which were killed, while in all the rabbits which died as a result of acute lead poisoning, there was a depletion of lymphoid tissue and in no case could germinal centres be found.

Changes in Spleen.

The absence of any signs of lymphocytic proliferation in the spleens of the six rabbits which died was in marked contrast to the abundant lymphoid tissue with many germinal centres present in sections of the seven rabbits which were killed. In five of the thirteen spleen sections many macrophages packed with brownish-yellow pigment, giving a positive result to the ferricyanide and hydrochloric acid test for iron, were observed.

Congestion of the pulp of the spleen was an outstanding feature in all except three sections.

Evidence of cell damage and cell destruction was obvious, particularly in the earlier sections in which many pyknotic nuclei and cell *débris*, both free in tissue spaces and contained in macrophages, were observed.

Sections from two rabbits taken two and two and a half days after lead injection showed many necrotic foci.

Changes in Lymph Glands.

There were similar changes in the lymphatic tissue in lymph glands. One rabbit in this particular series died as a result of acute lead poisoning and in a mesenteric gland from this rabbit there was an aplasia of lymphoid tissue with no germinal centres. In the five rabbits which were killed, there was a marked hyperplasia of lymphatic tissue with many germinal centres. In all sections there were many macrophages containing nuclear remnants and cell *débris* and in one section these cells contained much brown pigment giving a positive reaction for iron.

Discussion.

Since 1889 when Behrend first pointed out the association of punctate basophilia with lead poisoning, this phenomenon has received much attention and much investigation has been applied to it, but as yet the problem is still *sub judice*, although recent work done in Germany appears to throw light on the subject.

Ehrlich believed punctate basophilia to be of cytoplasmic origin, but Askanazy[38] in 1893 brought forward the hypothesis that the basophilic granules were nuclear fragments. Schmidt (1902)[39] and Cadwalader (1905)[40] were also of the opinion that the basophilic granulations were derived from the "dissolution of the nucleus of the red cell." The vital method of staining used by Cadwalader and the demonstration of these "basophilic granular cells" in normal blood as well as in anæmias, together with the description he gives of "fine and coarse thread-like strands," indicates that the cells described were reticular cells and not the stippled cells found in fixed films stained by Romanowsky methods.

This view, however, was accepted until Grawitz[41] in 1906 demonstrated that the granules were of cytoplasmic origin and that Ehrlich's hypothesis was correct. The evidence for the cytoplasmic origin of the granules is, firstly, that they are often present in cells with intact nuclei and, secondly, as far as is known, the granules have none of the characteristics of nuclear substance. They are transparent to ultra-violet light, while nuclear material is opaque, and they take a red stain with Pappenheim's methyl green pyronin, while nuclear material stains green.

The relationship of the basophilic substance in stippled cells to the basophilic substance in polychromatophilic and reticulated red cells has been the subject of much experimental work. Hawes[42] (1909) on the basis of comparative counts found that the percentage of polychromatophilic *plus* stippled cells was approximately proportional to the percentage of reticulated cells. Schilling-Torgan[43] observed that reticulated erythrocytes, if treated with very dilute alkalis and then stained supravitally, exhibited an appearance resembling punctate basophilia. Key[44] confirmed this and by varying the fixation in different parts of a blood film, was able to demonstrate in a single prepara-

tion all gradations between polychromatophilic cells, stippled polychromatophilic cells and stippled orthochromatic cells. Key also disproved the view that the reticulum was identical with mitochrondria by demonstrating differences in morphology, solubility and in resistance to a temperature of 50° C.

Brookfield,[17] using strengths of brilliant cresyl blue varying from 5% to 0·05%, showed a gradual transition from a complete reticulum in 5% to 0·2% cresyl blue to a fragmented reticulum and a granular deposit resembling stippling in 0·1% to 0·05% cresyl blue. He also demonstrated the presence of polychromatophilic cells only in fixed films of blood previously supravitally stained with brilliant cresyl blue below 0·05% in strength, while no polychromatophilic cells but only reticulated cells were seen if 0·2% to 5% solutions of brilliant cresyl blue were used. Brookfield states:

> There is little doubt that polychromatophilic and reticulated cells are fundamentally the same, the only difference being in the method of demonstration.

The relative number of stippled cells to polychromatophilic cells has been shown by various German investigators to depend largely on fixation factors. Schwarz and Kepke[45] found the number of stippled cells in films fixed with 96% alcohol was greater than in films fixed with absolute alcohol and Brückner and Spatz[46] found that the Maison Schwarz method of staining blood films revealed two and a half times as many stippled cells as were found with the Giemsa method. Brückner[47] demonstrated that if blood films of lead poisoned guinea-pigs were plunged into absolute alcohol while still moist or if the films were dried rapidly at a temperature of 60° to 100° C. and then fixed and stained, no stippled cells but only polychromatophilic cells were observed. He states with reference to air dried films that the relative number of polychromatophilic to stippled cells is a function of the temperature and moisture content of the air and he lays particular stress on the velocity of water abstraction from the cell as being a decisive factor.

This is about as far as our knowledge of the phenomenon of stippling extends. It would thus appear that stippled cells are cells containing basophilic substance which has been precipitated by the fixation and/or there may be an additional factor, such as a change in the basophilic substance effected by the lead, which renders it more readily precipitated as punctate basophilia.

The possibility that these immature cells are particularly susceptible to lead is indicated by the observation made in this study that immediately after an injection of lead there is a marked reduction in the reticular cell count. Another explanation is that the lead has a direct effect on the bone marrow, inhibiting the formation of red cells, and thus fewer immature forms are liberated into the peripheral circulation. The observation that the number of stippled cells had no apparent relationship to the number of reticulocytes or to the quantity of lead administered can be explained by Brückner's hypothesis that stippling is more or less an artifact produced by factors in the fixation of blood films.

The immediate fall in the red cell count would indicate that the lead has a definite destructive effect on the circulating red blood corpuscles and the marked fall in corpuscular volume with an almost constant plasma volume demonstrates that the anæmia is due solely to a depletion of red blood cells. Very little is known of the nature of the reaction of lead with red blood corpuscles. That there is a definite reaction is evidenced by the rapid depletion of these cells following an injection of lead and by *in vitro* experiments (Aub, Reznikoff and Smith[12]) in which lead has been taken up by red cells which are consequently affected in a particular manner, as is shown by their increased resistance to hypotonic saline solutions, by absence of agglutination when treated with appropriate group sera, by increased fragility and increased specific gravity.

Aub and Reznikoff[48] have postulated a chemical explanation of the reaction of lead with red blood corpuscles. They found that of the various known constituents of red blood corpuscles the inorganic phosphate alone could enter into chemical combination with lead and in the concentration normally found in serum and corpuscles neutralized the same quantity of lead as does whole blood. In the chemical action involved the very insoluble lead phosphate is formed with liberation of free acid. They considered that this acid could produce local changes at the cell surface, disturbing the colloidal properties of the cell membrane, so that the "leaded" red cell would be changed from an elastic distensible sac to one which was contracted relatively inelastic and brittle. That this is so is merely a conjecture and there is no evidence which reveals the exact nature of the reaction of lead with red blood cells.

With regard to the changes in blood volume, the most interesting feature, apart from the great fall in corpuscular volume, is the almost constant plasma volume. Bock[49] in a study of blood volume in various diseases, including polycythæmia, pernicious anæmia, chronic nephritis with œdema, cardiac failure with œdema and diabetes, found the plasma volume to remain constant except when the hæmoglobin was below 30%. It would thus appear that the maintenance of a stable plasma volume is of physiological importance to the organism.

It was shown that the red cell count showed a fall of 29%, while the corpuscular volume showed a fall of 43%. (This discrepancy was explained by a shrinkage in total blood volume and by smaller sized red cells.) Thus it is evident that the red cell count does not indicate the true extent of the anæmia, that is, if the plasma volume remains constant and there is a shrinkage in the total blood volume. If a constant plasma volume is invariable and if the plasma volume can be calculated with reference to body weight or body surface, then from the hæmatocrit the total corpuscular volume can be calculated. Changes in the total corpuscular

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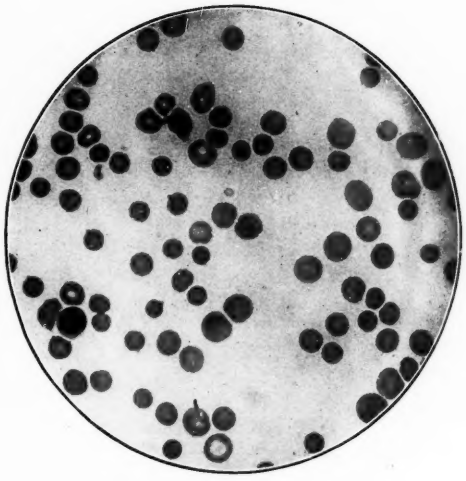

FIGURE I.
Blood film from Rabbit 3, taken seven days after lead injection, showing a normoblast, anisocytosis and poikilocytosis of the red cells. × 500.

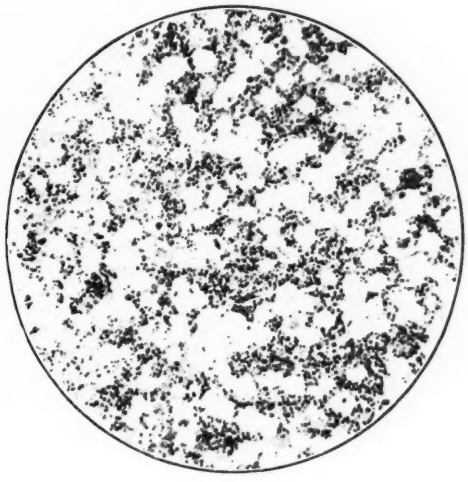

FIGURE III.
Bone marrow from Rabbit B, showing normal appearance. × 100.

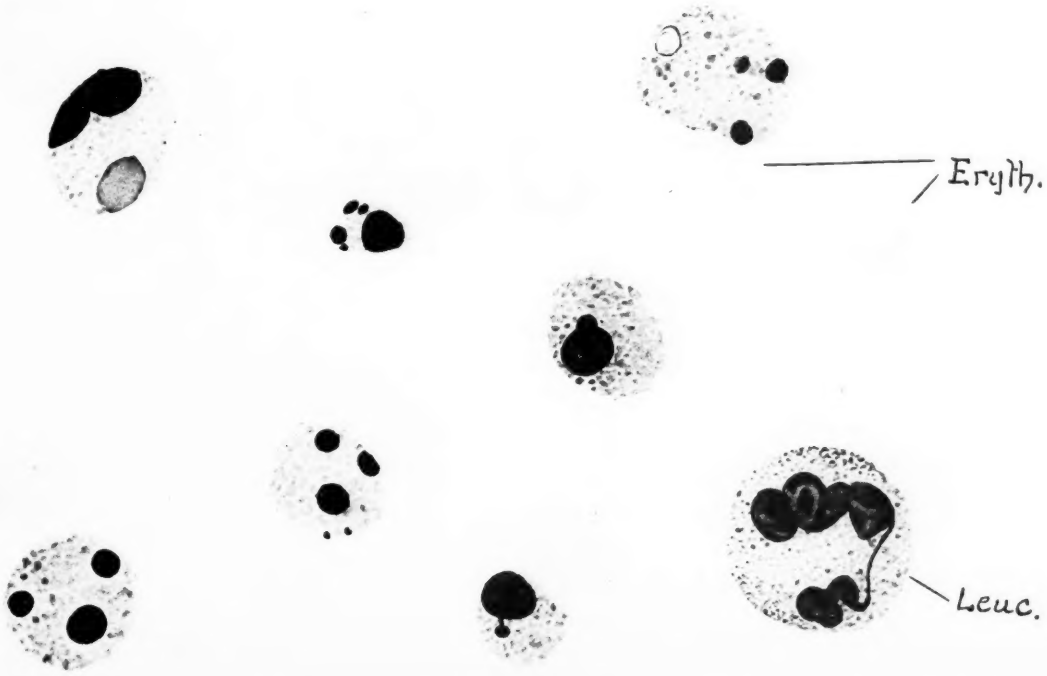

FIGURE II.
Showing degenerative changes in polymorphonuclear leucocytes. Leuc. = normal leucocyte. Eryth. = erythrocyte.

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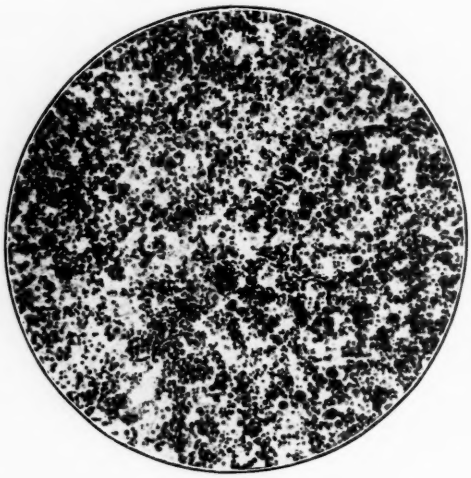

FIGURE IV.
Bone marrow from Rabbit 13A, showing congestion and absence of fat spaces. × 100.

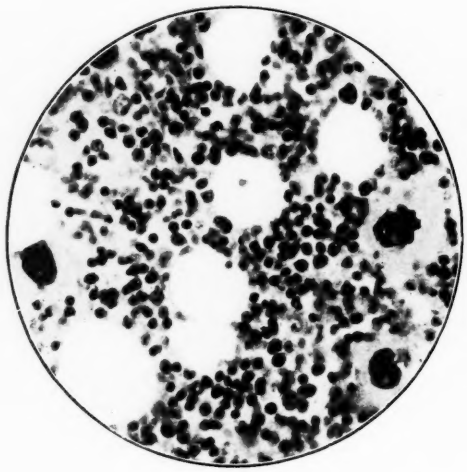

FIGURE V.
Bone marrow from Rabbit 14A, showing pyknosis of megalokaryocyte nuclei. × 400.

FIGURE VI.
Bone marrow from Rabbit 16A, showing congestion, disorderly arrangement of cells and pyknotic megalokaryocyte nuclei. × 100.

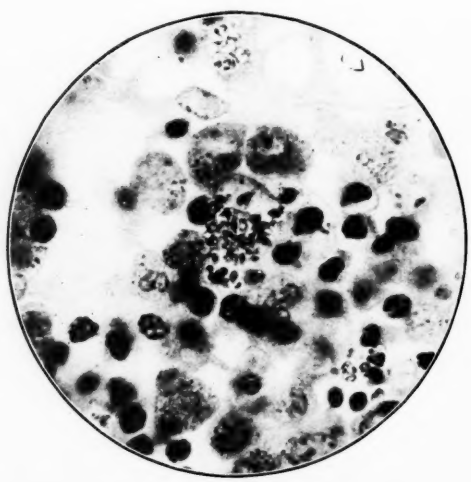

FIGURE VII.
Bone marrow from Rabbit 21A, showing pigment granules in a macrophage and pyknotic normoblast nuclei. × 1,000.

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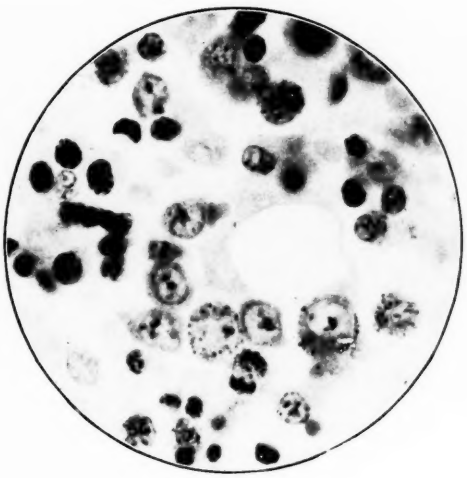

FIGURE VIII.
Bone marrow from Rabbit 12A, showing myelocytes and normoblasts with a mitotic figure in a myelocyte. × 1,000.

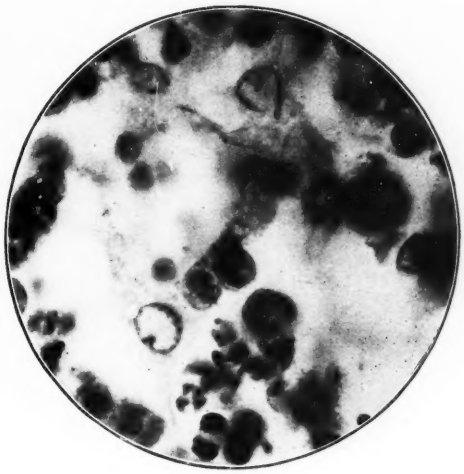

FIGURE IX.
Bone marrow from Rabbit 16A, showing reticular cells with pale swollen nuclei and fibrillated cytoplasm. × 1,000.

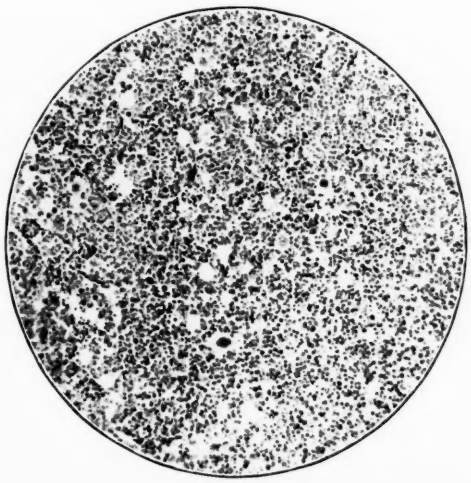

FIGURE X.
Bone marrow from Rabbit 10A, showing marked cellularity with myelocytes predominating. × 100.

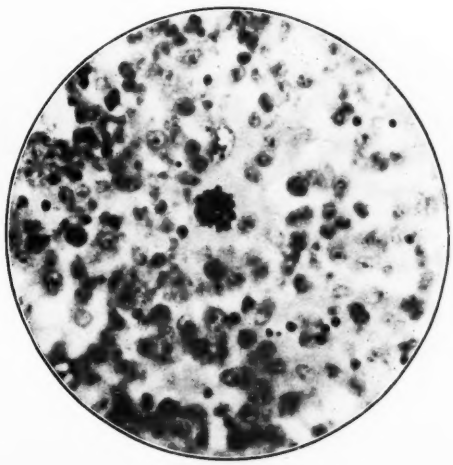

FIGURE XI.
Bone marrow from Rabbit 18A, showing a mitotic figure in a megalokaryocyte. × 400.

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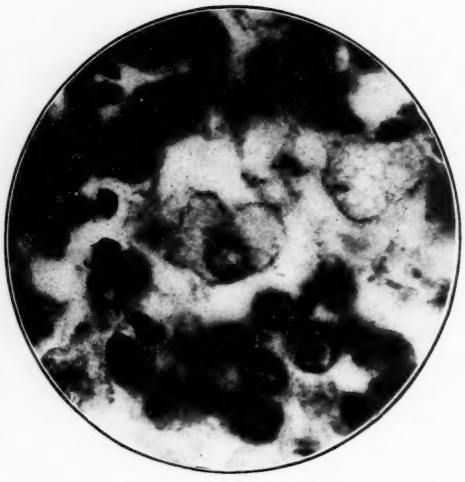

FIGURE XII.

Bone marrow from Rabbit 29A, showing cells of the reticulum with abundant cytoplasm containing numerous small vacuoles. × 1,000.

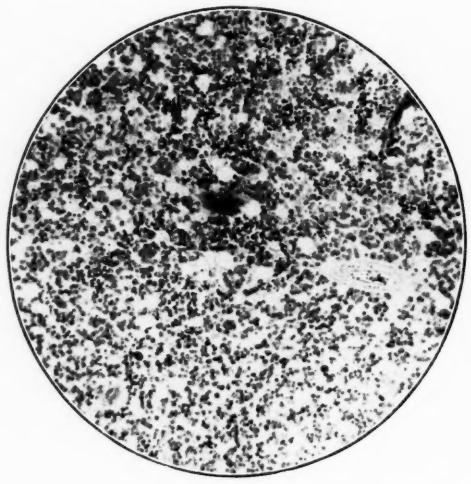

FIGURE XIII.

Bone marrow from Rabbit 8A, showing general hyperplasia of cells with myelocytes predominating. × 100.

FIGURE XIV.

Bone marrow from Rabbit 19A, showing cellular bone marrow with myelocytes predominating over normoblasts in number. × 100.

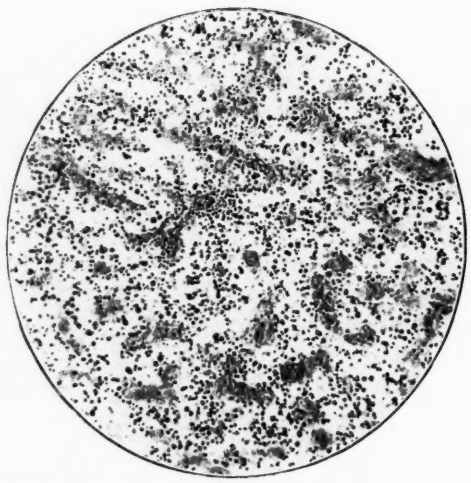

FIGURE XV.

Bone marrow from Rabbit 20A, showing dilatation of capillary sinusoids and infrequent blood forming cells. × 100.

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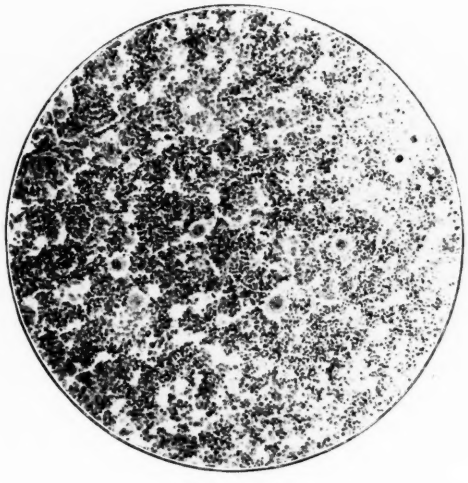

FIGURE XVI.

Bone marrow from Rabbit 23A, showing fewer myelocytes than in previous sections and an increased number of normoblasts. × 100.

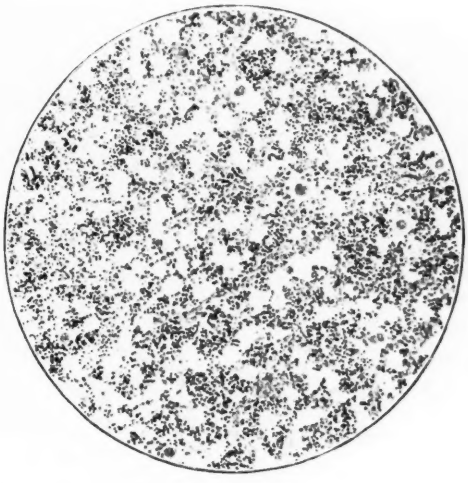

FIGURE XVII.

Bone marrow from Rabbit 22A, showing numerous normoblasts and reappearance of fat spaces. × 100.

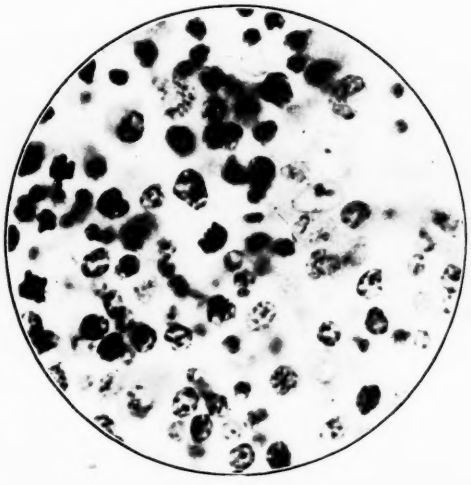

FIGURE XVIII.

Bone marrow from Rabbit 43A, showing many normoblasts in varying stages of maturity as indicated by pyknotic changes in the nuclei. × 1,000.

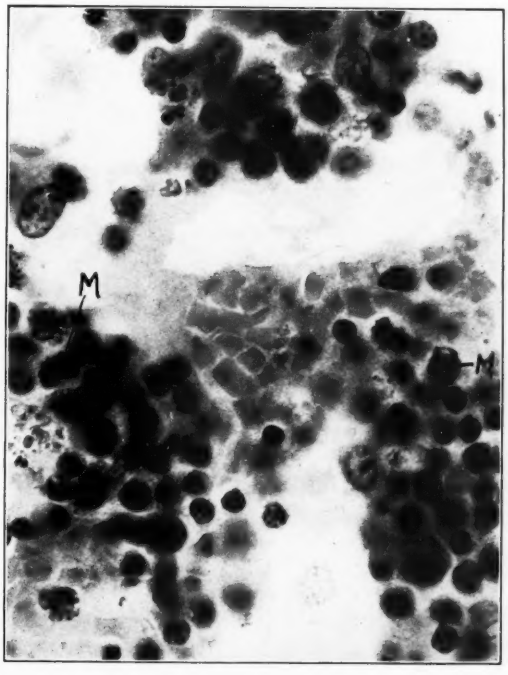

FIGURE XIX.

Bone marrow from Rabbit 38A, showing mitotic figures in groups of normoblasts. × 1,000.

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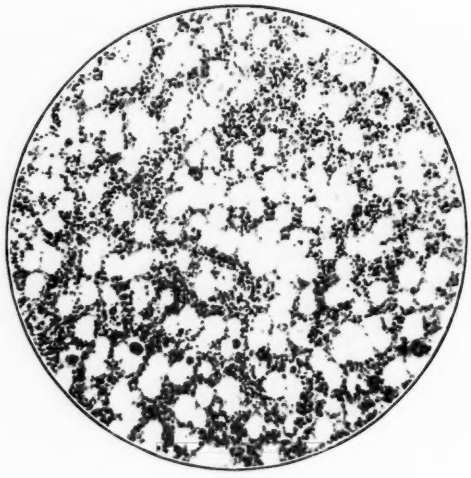

FIGURE XX.

Bone marrow from Rabbit 32A, showing many fat spaces and a return to the normal level of hæmatopoiesis, although there are more normoblasts in this section than in normal bone marrow (compare Figure III). ×100.

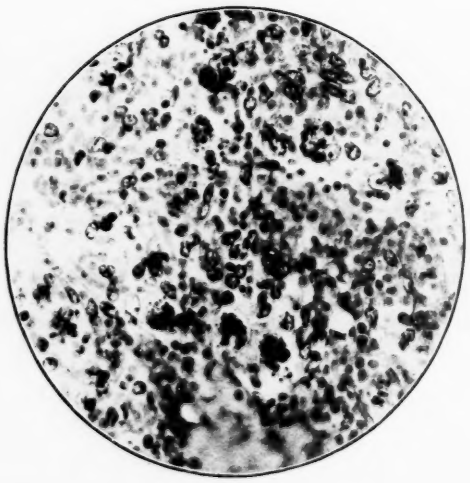

FIGURE XXI.

Spleen from Rabbit B1, showing pigment contained in macrophages. ×400.

FIGURE XXII.

Spleen from Rabbit 25A, showing a Malpighian body with abundant lymphoid tissue and several germinal centres. ×80.

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FIGURE XXIII.
Spleen from Rabbit 7, showing general fibrosis of pulp with scanty lymphoid tissue in a Malpighian body. × 80.

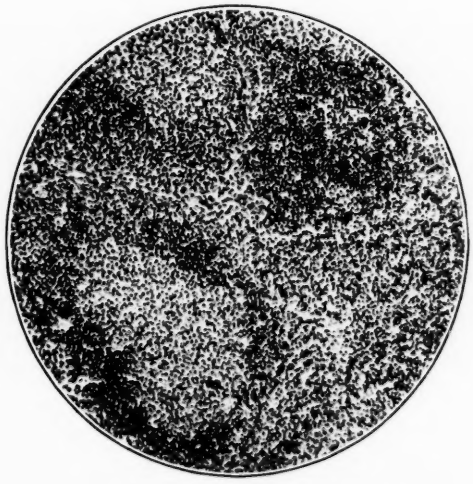

FIGURE XXIV.
Mesenteric lymph gland from Rabbit 45A, showing several germinal centres. × 80.

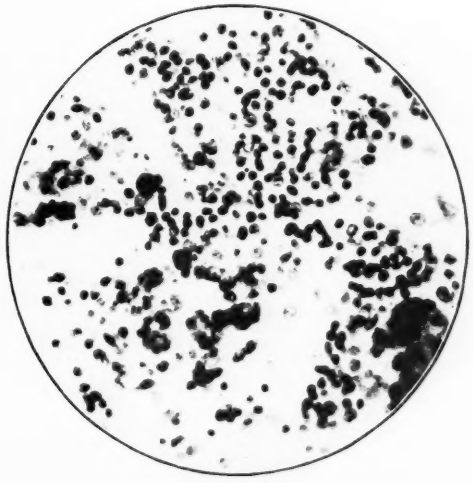

FIGURE XXV.
Mesenteric lymph gland from Rabbit 46A, showing macrophages containing pigment.

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volume are of much greater significance than changes in the red cell count and if it can be established beyond all doubt that plasma volume remains constant, then it is to be desired that red cell counts be superseded by hæmatocrit determinations.

Lead poisoning in rabbits, when induced by intravenous injection of a colloidal lead preparation, is characterized by definite changes in the white blood cells. The immediate rise in the leucocyte count could possibly be due to a purely physical effect of the colloid rather than a specific action of the lead, but this possibility can be excluded in view of the observation of Elvidge[50] that there is an immediate leucopenia following the injection of Indian ink, which may be regarded as an almost innocuous colloid.

The degenerative changes observed in neutrophile polymorphonuclear leucocytes and their rapid increase in number indicates that these cells were particularly concerned in the reaction against the lead, although their participation in the reaction may be only of such obvious significance in intravenous injections of lead. The immediate increase in metamyelocytes demonstrates that the bone marrow is actively responding to the invasion and is liberating leucocytes into the general circulation at an enhanced rate. This hypothesis is confirmed by examination of bone marrow sections. An interesting feature is the fall in eosinophile cells when the neutrophilia is marked and a subsequent increased number of these cells as the neutrophile cells fall in number. This finding is analagous to the post-infective eosinophilia which has been reported (Piney[51]). The significance of this increase in eosinophile cells is not known, although it has been suggested that associated with a post-infective lymphocytosis, it is concerned with the process of repair rather than with direct reaction. In these lead experiments the slight increase in eosinophile cells corresponds in time with the peak period of lymphocytosis.

The lymphocytes exhibit a greater response to the lead injections than do the polymorphonuclear leucocytes. There is a greater number of lymphocytes present in the peripheral circulation and this predominance in number is maintained during the period of seventeen days. The part played by the lymphocytosis in these lead experiments can only be guessed at. It has been observed by Nakahara and Murphy[52] in mice that the application of dry heat causes an increased production of lymphocytes. These workers have also shown that small doses of X rays produce a definite lymphocytosis, while larger doses produce destruction of lymphoid tissue. Clark[53] has shown that ultra-violet light incites a lymphocytosis. According to Whitney[54] it has been "repeatedly observed that as a disease overcomes the resistance of its host the lymphocyte count drops." It is supposed that the lymphocyte is associated in some way with resistance, but its exact rôle in that respect is still undetermined.

The blood platelets exhibit an immediate response to the lead injections. Brookfield[17] observed an immediate rise in platelets following injections of a preparation of colloidal lead similar to the one used in the above experiments, in patients treated for malignant disease. The action of the colloidal lead cannot be due solely to its physical properties, for Tait and Elvidge[55] have shown that the injection of various particles, including fine quartz particles, Indian ink, carmine and barium, is followed by an abrupt fall in the number of circulating platelets. Brookfield suggested that the rise in platelet count was due to a diminution in platelet destruction owing to a toxic effect of the lead on the phagocytic cells of the reticulo-endothelium. It is difficult to believe that such a mechanism is responsible for the very rapid rise in platelets. A more likely explanation is afforded from a study of the changes in the megalokaryocytes. Soon after lead injection these cells exhibited signs of damage and they were increased in number by over 100% during the period in which the platelet count was high and, subsequently, when the platelet count was normal, the count of these cells in the bone marrow was also at a normal level. Most present day hæmatologists accept the megalokaryocyte origin of the platelets enunciated by Wright[56] and in these experiments the apparent direct action of lead on the megalokaryocytes can be correlated with changes in the platelets in the peripheral circulation.

There is a striking reaction in the bone marrow to the injection of colloidal lead. The very marked proliferation of myelocytes which is particularly evident twelve hours after injection, when in one section the bone marrow was almost solely constituted with these granular cells, can be correlated with a neutrophilia in the peripheral circulation. It is remarkable that such a transformation in the morphology of the bone marrow could occur in such a short space of time. The early mobilization and proliferation of granular cells is in contrast to the slower and more sustained hyperplasia of normoblasts. Red cells have a greater expectancy of life than leucocytes. The duration of life of the red cell has been estimated from fifteen days to eighty-three days by different investigators (Krumbhaar[57]), while Sabin, Cunningham, Doan and Kindwall[58] demonstrated that 6% of leucocytes normally die in twenty-four hours. Thus the life of these cells is probably a matter of a few days. In emergency the hæmatopoietic tissue is capable of producing a large number of leucocytes at short notice as against a much slower output of red cells. The production of these latter cells is possibly greatly influenced by the hæmoglobin factor.

The most drastic change in the blood due to the injection of colloidal lead is the destruction of red cells in the peripheral circulation. Evidence of this red cell destruction is indicated in the bone marrow by the presence of an excessive amount of yellowish brown iron reacting pigment occurring free in the tissue spaces and contained in macrophages. For two or three days no other change with reference to the red cells is evident in the bone marrow and then a proliferation of normo-

blasts becomes marked and in ten days after injection the bone marrow was packed with immature nucleated red cells. These cells appeared in irregularly shaped groups and singly and many mitotic figures were observed.

Occurring *pari passu* with the proliferation of myeloid cells, is the disappearance of adipose tissue. This is a very necessary occurrence in the confined space represented in the shaft of a bone, but whether the disappearance of the fat has any other significance than to make room for the hyperplasia of the hæmatopoietic cells is a moot point. The single fat globule of the mature fat cell apparently breaks up into small globules and the cell then has an appearance simulating the embryonic fat cell. Doan, Cunningham and Sabin[67] have observed similar cells in the bone marrow of pigeons. They depleted the bone marrow of its hæmatopoietic elements by starvation and then the pigeons were given food and the changes in the bone marrow were studied. With the onset of regeneration of blood forming cells, fat cells were seen with "fat in droplets as it is in developing cells." It is probable that this change represents a removal of the fat from the bone marrow to allow hyperplasia of hæmatopoietic tissue. Whether the fat cells, when depleted of fat, take an active part in the prolific cell growth which is occurring in the bone marrow, is a point which calls for further investigation. It was rather interesting that in the bone marrow sections in which myeloid hyperplasia was predominant, fat spaces were not visible, but in sections in which normoblasts were predominant, fat spaces, although infrequent, were quite obvious. This could be explained by the theory of origin of blood cells propounded by Sabin. According to Sabin and her colleagues[59] the red cells arise intravascularly from endothelial cells, while the granular cells develop extravascularly. If such a theory is true, it would be possible that in increased red cell formation at a greatly enhanced rate, groups of developing normoblasts would dilate the capillary in which they were enclosed and would appear in sections as a mass of cells with definitely circumscribed shape. For instance, Figure XV shows a very congested bone marrow in which the capillaries were engorged with blood. The red cells can be recognized as occupying an intravascular position, not by the presence of a definite lining wall, but by their configuration. In a careful study of all the sections of bone marrow taken in these experiments and including many sections in which there was an intense proliferation of normoblasts, no such grouping of nucleated red cells could be made out; on the contrary, normoblasts were obvious everywhere in groups and occurring singly, but apparently subject to no such restriction as an enclosing endothelial wall.

In a consideration of the changes in spleen and lymph glands interest centres in the germinal follicles. The absence of germinal follicles and the scanty lymphoid tissue in all the rabbits that died, as compared with many germinal follicles and abundant lymphoid tissue in all the rabbits that were killed, is of significance. There is a difference of opinion as to the function of the germinal follicles. Flemming in 1885[60] put forward the view that these foci were the chief, although not the exclusive, places of multiplication of lymphocytes and he called them "germ centres." Since that time this conception has been generally accepted. However, Hellman[61] and others believe that they are of no importance for the regeneration of lymphocytes, but that they are reaction centres caused by irritative products from bacteria and other toxic bodies. Maximow[62] has criticized this conception and maintains that the principal function of the germinal centres is the production of lymphocytes.

In these lead experiments, according to Hellman's view, the presence of many germinal centres in the rabbits that were killed would indicate that the foreign particles of lead were being actively and successfully attacked, while in the rabbits that died the absence of germinal centres would indicate that there was no reaction against the lead and so the animal succumbed. According to Flemming's view, however, the apparent absence of resistance to the lead in the animals that died, could be attributed to a failure of the germ centres in regenerating a sufficient number of lymphocytes to protect the organism, that is, if we assume the lymphocytes have such a function.

The increase in lymphocytes in the peripheral circulation indicates that they play an important part in the reaction of the organism and such a lymphocytosis can be correlated with the presence of abundant lymphoid tissue and many germinal centres in the animals, which, until the time when they were killed, were successfully resisting the toxic action of the lead.

Conclusions.

1. The intravenous injection of colloidal lead causes an immediate fall in the red cell count and hæmoglobin.

2. After the first injection the reticulocytes do not increase in number so rapidly as would be expected with such a fall in red cells and after subsequent injections of lead the reticulocytes are temporarily diminished in number. This is possibly due to a direct effect of the lead on reticulocytes.

3. There is a very marked fall in corpuscular volume and practically no change in plasma volume, indicating that the anæmia is due solely to a depletion of red cells.

4. After an injection of lead there is an immediate leucocytosis which is due at first to a neutrophilia. After eight hours the lymphocytes and large mononuclear cells begin to increase and in two days these cells have reached a higher maximum than the granular cells. Subsequently the white blood cells gradually diminish in number and the non-granular cells remain in excess of the granular cells throughout the period of the experiment.

5. There is an immediate abrupt rise in the platelet count which after twelve hours is followed by a more gradual decline to the normal level.

6. Within twelve hours after the injection of lead, corresponding with the neutrophilia in the peripheral circulation, there is in the bone marrow a very marked proliferation of myelocytes. Subsequently this hyperplasia of granular cells becomes less marked.

7. Following the injections of lead the megalokaryocytes show signs of damage and correlated with a high platelet count in the peripheral circulation there is an increased number of megalokaryocytes in the bone marrow.

8. Fat spaces disappear *pari passu* with the hyperplasia of hæmatopoietic cells and at twelve hours after injection fat cells appear to have undergone a marked change. The nucleus of the cell is round in shape and is in a central position and the abundant cytoplasm is branching and is packed with tiny fat globules. Such cells at this period appear to constitute the reticulum of the bone marrow. These cells are in evidence until the hyperplasia of blood forming cells diminishes and then the globules appear to become larger and ultimately mature fat cells are alone present, while hæmatopoiesis is back to a normal level.

9. Evidence of red cell destruction was demonstrated by excessive amounts of iron reacting yellowish-brown pigment, contained in macrophages and present free in the tissue spaces, in spleen, bone marrow and occasionally in lymph glands. In the early stages particularly there was also nuclear and cytoplasmic *débris* in a similar location in these tissues.

10. Normoblasts begin to proliferate two to three days after lead injection at a period when the hyperplasia of granular cells is beginning to subside and an excessive multiplication of normoblasts is maintained for at least fourteen days.

11. There is an absence of germinal centres and an aplasia of lymphoid tissue in spleen and mesenteric lymph glands of the rabbits that have died as a result of acute lead poisoning, while in the rabbits that were killed there are many germinal centres and abundant lymphoid tissue.

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Reports of Cases.

LARGE ADENO-CARCINOMA OF PITUITARY GLAND TREATED BY OPERATION.

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AND
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CLINICAL HISTORY.

(L. A. HAYWARD.)

ON July 12, 1927, a somewhat gigantic young man of thirty consulted Dr. Hayward. His occupation was farming and he was unmarried. He complained of pains in the back, severe headaches, weakness in the legs and shortness of breath. His feet swelled and his hands went quite blue in cold weather. His sight was beginning to suffer and he had occasional diplopia. These symptoms had been developing for eighteen months.

On examination he was a very large man weighing 111·6 kilograms (seventeen and a half stone), of sallow complexion, with the general appearance of acromegaly—large head, prominent frontal sinuses, broad face, prominent chin, huge spade-like hands and feet. The heart sounds were normal, but rapid, the pulse rate being 104 at rest. The systolic blood pressure was 170 and the diastolic pressure 90 millimetres of mercury.

The urine contained no albumin. The blood sugar was slightly above the physiological normal. The blood picture was as follows:

Red cells, per cubic millimetre	6,300,000
Hæmoglobin value	80%
White cells, per cubic millimetre	14,000
Polymorphonuclear cells	60%
Hyaline cells	13%
Lymphocytes	24%
Eosinophile cells	3%

Dr. Herbert Moxon saw the patient and added the following notes:

> The patient had dysentery in 1918 in Italy and was treated with emetine. He had no other past illnesses. The patient was not normally bright and alert. On examination of the eyes the reflexes were normal. There was apparently a definite hemianopia in the temporal field of vision of the right eye. The patient objected to bright light. The hair is coarse and thick. The tongue is dirty and very furred. The teeth are all artificial. There is no tonsillar sepsis. The ears are apparently set far back. The lips are thick. The skin is normal, not unduly hairy. Nothing abnormal is found in lungs or abdomen.
>
> On examination of the nervous system the deep reflexes are all sluggish, some are not elicited. The abdominal and cremasteric reflexes are normal. The cranial nerves, excepting the optic, are normal. There is neither motor nor sensory change. There is no history of polyuria. The patient is not subject to sweats.

Dr. Donald Smith made an X ray examination of the skull and his report is as follows:

> There is definite evidence of pituitary tumour . . . expanded *sella turcica* in fairly uniform manner in all directions. The walls of the sella have been thinned out extensively, the posterior clinoid processes have disappeared, but the anterior clinoid processes are very attenuated and pushed laterally until they lie 2·5 centimetres (one inch) apart. The sphenoid sinus has been flattened in a forward direction. These appearances, combined with thin osteophytic membrane around the base of the tumour, indicate that it is probably benign. There is no evidence as to what extent the tumour rises above the level of the floor of the skull into the cranial cavity. Note the large frontal sinuses.

The X ray appearances are seen in the accompanying illustration.

Dr. C. Morlet examined the patient's eyes. He saw the patient first on August 1, 1927. At that time the acuity of vision was: Right eye, $^6/_{36}$; left eye, nearly $^6/_6$. The fields showed typical bitemporal hemianopia associated with pressure or traction at the optic chiasma. The hemianopia was almost complete on the right side, but involved only a comparatively small area of the left temporal field. A general contraction of both fields was also evident, involving especially the field for red on the left side. Both discs showed evidence of atrophy. On the right side pallor was associated with considerable cupping or loss of substance. On the left side there was pallor of the disc, but with little cupping and therefore presenting a more favourable prognosis as regards possible recovery of vision. Dr. Morlet thought that atrophy of the nerve head indicated severe or long continued pressure or traction upon the nerve in its course and that prognosis depended on the amount of permanent danger done, as opposed to physiological block, offering a chance of recovery of function after relief of pressure.

Dr. Morlet saw the patient next on September 26, 1927. No change had taken place in visual acuity nor in appearance of discs. No change was detected in the temporal hemianopia of the right side which was still almost complete. A definite shrinking was noticed in the blind area of the left temporal field which was never very extensive. The patient was able to read printing slowly and with difficulty. Unfortunately Dr. Morlet has not since seen the patient.

THE OPERATION AND COMMENTS.

(THEODORE AMBROSE.)

After the patient was seen in consultation a diagnosis of enlarging pituitary tumour was made. An operation was decided upon and performed on August 9, 1927. Excellent ether anæsthesia was induced by the intratracheal method by Dr. Gilbert Troup and Dr. Hayward very ably assisted.

A large frontal osteoplastic flap was reflected; owing to the huge size of the frontal sinus, this presented unusual difficulty, but a compromise was made by chiselling away the anterior wall of the sinus and reflecting the posterior wall with the flap. There was also the added risk of sepsis from the nose through direct access to the field of operation by way of the *infundibulum*. The reflection of the flap was a formidable undertaking. The skull was quite 1·25 centimetres (half an inch) thick, the diploetic layer was greatly enlarged, numerous small arterioles bleeding freely therefrom. The scalp was affected by a condition approaching cirsoid aneurysm. Much time was spent in endeavouring to arrest hæmorrhage from the scalp and skull, but nevertheless bleeding continued freely throughout the operation, in fact the amount lost was quite appalling, enough to have killed a smaller subject. Very little trouble or hæmorrhage occurred in the intracranial part of the procedure; the *dura mater* was incised and the frontal lobe raised until a large rounded swelling presented in front of the optic chiasma. This was opened and a large quantity of brain-like contents was curetted gently away until all was removed; oozing from the cavity was controlled by temporary gauze packs steeped in adrenalin solution.

The anterior portion of the frontal lobe was a little roughened by the gauze pads used to protect the brain during retraction; otherwise no apparent injury was caused to the brain. One bleeding anterior cerebral vessel had to be undersewn.

The *dura mater* was carefully sutured and then the operation area was well irrigated. A little iodoform powder was dusted on the cut bone and into the internal angle of the frontal sinus. A small rubber drain was inserted at the antero-internal angle of the wound.

During the operation the patient swallowed several ounces of blood which passed through a large *infundibulum* into the naso-pharynx; this was mostly vomited.

A suction apparatus was employed to keep the operation area at the base of the brain dry and retractors electrically lighted gave good vision in the deeper work.

At the conclusion of the operation the pulse rate was 120, the diastolic and systolic blood pressure only 40 and 65 millimetres of mercury respectively. The patient was moderately shocked, but picked up well. The pulse rate had fallen to 100 three hours after operation.

Fifteen hours after operation the patient spoke rationally, but through the day, although the pulse improved, the mental condition was disturbed and great irritability was manifested. Large quantities of water were imbibed and a great craving for beer was present. The temperature varied from 37·8° to 39·4° C. (100° to 103° F.). Glucose and saline solution were given freely *per rectum* and "Pituitrin" hypodermically every four hours.

Very little urine was excreted for the first twenty-four hours. On the second day great œdema of both eyelids occurred, closing the eyes completely. The patient was less thirsty, but restless and irritable. Bromide was given freely. There was no sugar in the urine.

On the fourth day the patient's general condition had improved and his mental condition was better. The rubber drain was removed, as there was no discharge. The temperature, however, ranged from 37·8° to 38·9° C. (100° to 102° F.) for a few days until a large discharge of pus brought it down. Thereafter his condition steadily improved; the wound did not heal absolutely for some four months, when a small sequestrum came away.

After the first few days he was able to read comfortably, which he had been unable to do for some months before operation. His skin was always cold and usually wet with perspiration; otherwise there were no distressing symptoms.

The patient after six months resumed his work as a farmer; he also took unto himself a wife.

His last report to Dr. Hayward some two years after operation stated that his general strength was much improved, though not quite normal. He could work about five and a half days a week. He had been working for twelve months at such hard labour as tractor driving and wheat carting. He felt the necessity of an occasional day's rest. He had slight headache occasionally. His sight was good. His sexual power was quite normal at times, sometimes below par. There is now no dyspnœa on exertion; his hands and feet have not altered in size or shape, his weight is 100·8 kilograms (sixteen stone).

Dr. S. McConnell's report of the tumour was that of an adeno-carcinoma of the pituitary gland.

Comment.

The special features of this case were: First, the operative difficulties presented by the excessive hæmorrhage from the scalp and skull and the presence of the greatly enlarged frontal sinus. Secondly, the very considerable sexual power retained by the patient.

Cushing's results show a very small percentage of patients with any degree of sexual power after operation. As to the nature of the tumour the microscopical appearance of pituitary tumours is apparently not always in harmony with the clinical picture. Many so-called adenomata are malignant in nature—they perforate the capsule and infiltrate the brain. On the other hand, as in this case, the growth microscopically was a typical adeno-carcinoma, but up to date has shown no sign of recurrence.

ACKNOWLEDGEMENTS.

We wish to thank Dr. Moxon, Dr. Hislop, Dr. Morlet and Dr. Donald Smith for clinical notes; also Dr. F. Clark, Dr. H. B. Gill, Dr. F. L. Gill, Dr. Hadley and others for advice and the loan of special apparatus.

Reviews.

TALES OF SURGICAL PROWESS.

WHETHER or not "The Dramatic in Surgery" surpasses in interest the tragic, the humorous or other competitors, Mr. Gordon-Taylor has presented a delightful little book.[1] In the preface it is explained that, after hearing his lecture to the Surgical Society of Manchester in 1928, some of the audience requested him to have it published in book form. Many of the wonderful deeds of modern surgical work are here displayed, not for the glorification of the author, but for the collective publication of clever feats performed by dexterous surgeons to whom the author has given due credit. The lay mind rejoices in the works of Edgar Wallace and the medical will be pleased with the narration of these dramatic instances.

War experience has been extensively drawn upon in connexion with abdominal and thoracic wounds. The reader learns of a bullet successfully extracted from the inferior *vena cava*, of an embolus removed from the pulmonary artery, of a secondary myeloma excised from the lung after artificial pneumothorax. Attention is directed to the number of yards of the alimentary canal that may be dispensed with, and the almost superfluous viscera we possess.

Nature is kind to the surgeon, if he is not unkind to her. This collection of uncommon instances of surgical courage and dexterity provides the reader with an enjoyable hour's entertainment and instruction. Not only so, but for the more inquisitive a list of references points the way to an investigation of the details of many of the case histories. The small book is well illustrated and written in a happy vein.

Notes on Books, Current Journals and New Appliances.

A WAR STORY.

"NOT SO QUIET," by Helen Zenna Smith, is another of the war stories that appear to be fashionable at the moment.[2] It is supposed to be a "plea for the ultimate crushing of such dishonest and reasonless beastliness that gambles with the souls and bodies of men and women, that steeps humanity in foulness, that wrecks the entire world, and mocks at creation." It is supposed to be written by an ambulance driver in France. The author has collected every scrap of frightfulness that she could muster and written it into a book. She has repeated herself time and time again and she has added quite a lot of unnecessary vulgarity. The latter makes us question the sincerity of the motive. At the same time the book compels interest; parts of it are extremely well written and the psychological insight of the author is often profound. If she had wished to present a true picture, she would have introduced more evidence of the ennobling effect on character of devotion to duty and service to others. The book is worth reading, but as antiwar propaganda we fear that it and books of its kind are useless.

[1] "The Dramatic in Surgery," by Gordon Gordon-Taylor, O.B.E., M.A., F.R.C.S.; 1930. Bristol: John Wright and Sons Limited; London: Simpkin Marshall Limited. Royal 8vo., pp. 88, with 40 illustrations in the text, 11 of which are fully coloured. Price: 12s. 6d. net.

[2] "Not so Quiet," by Helen Zenna Smith, 1930. London: Albert E. Marriott Ltd. Crown 8vo., pp. 240. Price: 6s. net.

THE BEHRING-VENULE.

FROM Bayer Products, Limited, 19, St. Dunstan's Hill, London, E.C.3, we have received samples of the "Behring-Venule," an automatic aspirating syringe for the collection of blood and other body fluids for pathological investigation. It is always ready for use, of assured sterility and it functions automatically.

The ordinary venule consists of a strong glass tube of eight cubic centimetres capacity, from which the air has been exhausted; it is closed by a perforated rubber stopper carrying a thin glass tube containing a sharp steel cannula. The glass tube passing through the rubber stopper is bent at a right angle in such a manner that the short limb has its open end pressed against the inner wall of the rubber stopper. The contact between the glass tube and the stopper thereby forms a sort of valve which is kept constantly closed by the elasticity of the rubber. This valve is opened by firm pressure on the angle formed by the glass tube and the receiver.

The skin of the anticubital region is carefully cleansed with antiseptic, a tourniquet or bandage is placed around the upper arm in order to impede the venous return, the vein is then entered in the direction of the venous flow. As soon as the blood is seen in the capillary between the needle and the rubber stopper the vein has been successfully entered and the valve may be opened.

Special sealing of the venule after filling is not necessary because the valve is self-acting. When the receptacle is full, the small glass tube is scratched with a file at its junction with the stopper and broken off. The venule is now ready for dispatch. If the fluid is infective, as an additional precaution the end of the broken tube may be warmed and sealed with a dab of sealing wax or paraffin wax. Venules of special types are obtainable for the transfer of blood to a pathologist. Others contain nutrient broth and other media. Venules are supplied in tin tubes and wooden boxes which conform to the postal regulations.

A LARYNGEAL MUCUS EXTRACTOR.

IN *The Lancet* of April 12, 1930, Dr. A. B. Rufail describes an apparatus by which mucus can be extracted by suction from the mouth of an infant without any risk of its reaching the mouth of the operator. It comprises two portions of metal tubing connected by an intermediate chamber, itself divided into two parts which can readily be separated for cleaning. Within the upper portion or lid of the chamber is a detachable baffle in the form of a conical disc or dome provided with a U-tube, one end of which passes through the centre of the dome and screws into the suction tube, whilst the other end terminates on the upper surface of the dome and this dips into an annular recess in the lower portion of the chamber. The instrument is made by Allen and Hanburys, Limited.

The Medical Journal of Australia

SATURDAY, JULY 5, 1930.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: Initials of author, surname of author, full title of article, name of journal, volume, full date (month, day and year), number of the first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction, are invited to seek the advice of the Editor.

DIAGNOSIS.

WHILE the importance of making an accurate diagnosis as a preliminary to the successful treatment of disease is widely recognized, some medical practitioners would possibly find it difficult to discuss the essential qualities of the diagnostician and to lay down the principles on which he should act. The discovery of some of the newer methods of clinical examination and the introduction of present day laboratory tests have doubtless simplified many of the problems of differential diagnosis, but they also tend to give rise in the mind of the student to the impression that diagnosis is a matter of exclusion or confirmation by test tube or microscope. Emphasis on the infecting microorganism or virus has turned attention from the older views on diathesis and the study of the patient as an individual has been neglected.

It has been pointed out by many of the older writers that diagnosis is partly a science and partly an art—a science because it has to do with facts and principles based on those facts, and an art because it demands a cognizance of certain methods and their application before a definite decision can be made. The first step towards making a diagnosis is a consideration of the patient's symptoms. All clinical histories are not easy to elicit and sometimes it may be impossible to obtain a connected story of the onset and progress of the illness. When an account of the symptoms has been obtained, it must be sifted and subjected to careful scrutiny in order to discover whether anything material has been omitted or whether any attempt has been made to deceive. From a clear account of symptoms important facts may be deduced and these must be correlated with the findings on physical examination. It is necessary to emphasize the importance of an ability to recognize morbid signs. This, of course, implies a knowledge of the normal. The art of observation is not always easy; to many people it is a natural attribute, others have to cultivate it by continual practice. For the recognition of many abnormal signs special methods of examination are required and special apparatus. It is here that the laboratory test and microscopical examination find their place. For the interpretation of signs and symptoms a knowledge of pathology is necessary. It must be known why and how a certain abnormal manifestation is brought about and what are the causes of conditions likely to be confused with the one under consideration. The clinician must be able to bring logical reasoning ability to his aid. Sometimes the process is simple and he has to reason on ascertained facts alone, but sometimes he has to reason from premisses which are mere probabilities. Diagnosis may thus be made by direct methods—a certain disease is present because distinctive features have been noted and these features are typical of a certain condition only. Or diagnosis may be made by a method of exclusion—the patient's condition cannot be due to a certain type of infection because certain features are absent and it can be due to only one remaining condition which might cause the clinical manifestations. Of the two methods the former is obviously the more exact and is to be sought whenever possible. It is by no means always possible. In endeavouring to make any diagnosis the clinician must be mindful that there is such a thing as diathesis and that the psychological condition of the patient may colour the picture to no inconsiderable extent. Thus it may be concluded that, if he is to be an expert diagnostician, the medical practitioner must have a knowledge of semeiology, must be gifted with

powers of observation, must have a knowledge of pathology and laboratory methods, must have a logical mind and must endeavour to gain a certain psychological insight.

In order to help the general practitioner to overcome his diagnostic difficulties, a series of special articles on diagnosis will be published in this journal. The first appears in this issue. These articles are contributed by request and will deal with subjects of everyday interest to the practitioner. The authors have been chosen because of their known interest in their respective subjects and of their ability to express their views to others. This opportunity is taken of thanking them for their work. Readers of the journal are asked to show their appreciation by careful study of the articles as they appear.

Current Comment.

ENCEPHALITIS PERIAXIALIS DIFFUSA.

IN 1867 Virchow described a condition which he termed "congenital interstitial encephalitis." The picture he painted was essentially that of the disease now known as Schilder's disease or *encephalitis periaxialis diffusa*. Probably he was the first to recognize it as a definite entity. Schilder in 1912 gave a complete description of the disease and gave it its modern title.

Though it is chiefly a disease of childhood and adolescence, no age appears to be immune; its occurrence in an infant of six and a half months and a man of seventy-seven years has been reported.

The chief pathological feature is a widespread, diffuse, though sharply-defined, degeneration of the subcortical white matter of the cerebral hemispheres. Both halves of the brain are usually more or less equally affected. According to Schilder the myelin sheaths suffer degeneration, while the axis cylinders remain relatively unaffected. It is now known that the axones become profoundly involved in the later stages, hence the qualification "*periaxialis*" is incomplete. Proliferation of the glial cells is a feature and the *débris* of the degenerated nerve fibres is disposed of by phagocytosis. There is a well marked perivascular lymphocytic infiltration in the affected areas. The degenerative process appears sometimes to result in softening, sometimes in hardening of the white matter. Conceivably such apparent inconsistency may depend on whether the proliferative or degenerative changes predominate, on the rapidity of the progress of the disease and on the stage to which it had advanced before death.

As the disease frequently commences in the occipital lobes, blindness is an early, though not an invariable, symptom. Secondary optic atrophy occurs rarely and a moderate papillœdema has been reported on some few occasions. As a general rule, however, the fundus presents a normal appearance and the signs are those of a central blindness. Homonymous hemianopia may occur in those rare instances of unilateral disease. Spastic paralysis and progressive amentia are conspicuous symptoms. Deafness is common; convulsions are usual. There is no fever. The shortest duration of the disease in any recorded instance was a few days, the longest thirteen years; on an average its course occupies a period of about ten and a half months. Death is inevitable and occurs in coma. Nothing is known of the ætiology.

The most notable communication on the subject in the British literature is that of Collier and Greenfield which appeared in *Brain* in 1924 (Volume XLIX, page 489). Earlier in the same year Bouman had presented a report which was the first recorded in the English language.

A complete review of the literature and an excellent description of the disease as seen by him in one instance has recently been made by Benjamin M. Gasul, of Chicago.[1] His patient, a white boy, aged eight years, died after an illness lasting for some three months. The child had been quite well prior to the onset, which was marked by vomiting and headache. Later there appeared difficulty in speaking which went on eventually to complete motor aphasia. Spastic paralysis of the right extremities developed and later spastic paresis on the left side. Gasul remarks that the child appeared to understand what was said to him, but he makes no further mention of the mental condition. He states that there was no apparent impairment of sensation and that the cranial nerves were unaffected. Nothing abnormal was detected on examination of the blood and urine. The cerebro-spinal fluid was clear and under normal pressure. The Wassermann test applied to the cerebro-spinal fluid gave no reaction.

Examination of the brain *post mortem* was made by Dr. R. R. Grinker. The meninges were injected. The surface configuration of the brain was normal. A widespread softening of the white matter of the parietal lobes extended on the left side as far forward as the middle frontal convolution and on the right side to the level of the anterior end of the caudate nucleus. The *corpus callosum* was involved to some extent. In the frontal lobe on either side was a grey area which had not become appreciably softer. This is regarded as the earliest change seen. Though there was injection of the vessels of the cerebellum, the white matter of neither cerebellum nor cord was in any way affected. In the parts where the disease appeared to be most advanced, both myelin sheaths and axis cylinders had completely disappeared; in the more recent areas, remnants only were discoverable. Abundant proliferation of glia cells was evident in the earlier lesions; in the areas later affected, degenerating cells and phagocytic cells containing fat globules could be seen; in the final stages the degeneration

[1] *American Journal of Diseases of Children*, March, 1930.

appeared to have proceeded to vacuolation and complete disintegration of the normal cells of the glia. The blood vessels did not appear to be early affected, but in areas where the disease had become well established, they were surrounded by fat-containing cells and lymphocytes.

Gasul remarks that in his patient the disease was atypical in that the changes were practically confined to the parietal lobes, and that the occipital lobes were unaffected. He points out that the greatest difficulty in classifying Schilder's disease lies in determining whether its essential nature should be regarded as inflammatory or degenerative. He believes the answer may be found in a study of the blood vessels. In his experience perivascular infiltration occurs only in the softened areas and is apparently of the nature of a response to damage rather than an inflammatory reaction against invasion by a virus. Furthermore, the cortex and white matter obtain their blood supply from different sources and the abrupt transition from healthy cortex to profoundly affected white substance is a striking feature of the disease. He suggests that the disease is a degenerative condition due to some disturbance of the vascular supply of the white matter.

It must be pointed out that Adie believes that the encephalitic group of diseases is caused by a filter-passing virus; he includes disseminated sclerosis in the encephalitic group. This is of interest in view of recent work on disseminated sclerosis by Chevassut, described in these pages in the issue of June 14, 1930. The acceptance of Gasul's view would necessitate a change of name, for encephalitis cannot be applied to a non-inflammatory degeneration. The vascular disturbance postulated by him might and probably would be the result of an infective process.

Doubtless, deaths due to *encephalitis periaxialis diffusa* have occurred in Australia, but as far as can be discovered, the only one reported in Australian literature appears in the recently issued first number of *The Melbourne Hospital Clinical Reports* and is from the pen of Maudsley and Wright-Smith. The condition is of interest to the ophthalmologist, otologist, physician and surgeon and merits further study. Its recognition is important in view of the likelihood of the institution of unnecessary surgical procedures, should a diagnosis be made of cerebral tumour with which it may possibly be confused. Though reports of only seventy-one cases appear in the literature, the disease is probably not nearly so rare as this figure would appear to indicate. Its presence should always be suspected when there is spastic paralysis associated with blindness or deafness and mental impairment.

DIATHERMY IN PUERPERAL SEPSIS.

THE general tendency to apply to many and divergent conditions a therapeutic agent which has been the means of achieving good results in one or two, is exemplified in the present vogue for diathermy. No one will deny that the application of heat will often relieve pain nor will it be gainsaid that the hyperæmia resulting from use of diathermy is capable of doing much good in many pathological states. Those who are wise, however, will insist on the most searching investigation and rigorous control before any general statement in regard to therapeutic benefit is accepted and before diathermy is adopted as a routine treatment in any condition. For example, it has been claimed by many that diathermy is a valuable agent in the treatment of pneumonia, reports of successes have been published and books have been written on the subject; but there is something to be said for the views of those who admit that benefit is obtained and at the same time ascribe that benefit, not to any local effect on the lung, but to relief of pain and increase of resistance due to a production of a feeling of general well-being.

It is thus with caution, if not with scepticism, that readers should consider a recent report by C. A. Robinson.[1] Robinson has used diathermy in the treatment of twenty-one patients with puerperal septicæmia at the West Middlesex Hospital. The method of application was by means of a vaginal electrode and lead belt "as used for intrapelvic heating for inflammation of the pelvic contents." Six patients recovered after abscess formation, eight recovered by lysis and four by crisis; there were three deaths. Of the three patients who died, one was moribund before diathermy was begun, one died from pulmonary embolism after crisis had occurred and the third died from septicæmia following abortion and not full term confinement. All the patients are described as being very ill and Robinson is convinced that without the intervention of diathermy most of them would have died. This is, of course, merely an opinion—the opinion of an enthusiast — and may or may not be correct. Robinson gives no data as to the current used, the number of treatments, their duration or the intervals between them. In considering his results there is ample room for scepticism as to the good achieved by the diathermy. In the first place the series is small. Puerperal septicæmia is difficult of prognosis, the most surprising and the most disappointing things happen in its presence. These patients might have got well without any treatment, Robinson's opinion notwithstanding. In the second place he has found that in sapræmia diathermy is not only useless, but dangerous, for if putrefying material in the uterus is heated, the output of toxins is increased and toxæmia is also increased. It is impossible to say where sapræmia ends and septicæmia begins in any particular infection. If septicæmia is established, there is neither reason nor justification for heating the uterus by an electrode introduced into the vagina.

[1] *Proceedings of the Royal Society of Medicine*, December, 1929.

Abstracts from Current Medical Literature.

PÆDIATRICS.

Encephalo-Myelitis Following Vaccination.

J. GRAUBARTH (*Archives of Pædiatrics*, November, 1929) reports a case of encephalo-myelitis following vaccination. This condition has been recognized only during recent years. The pathology has been definitely established by Turnbull and McIntosh. The gross changes are slight and consist merely of some congestion of the meninges and a few red spots on the cut surface of the cord. Microscopically, in the acute stage, an inflammatory process is found throughout the whole central nervous system. The chief incidence is in the lumbar enlargement of the cord and in the *pons*. The grey matter is more severely affected than the white, but both may show grave injury. All the smaller vessels are surrounded by collections of lymphocytes, plasma cells, leucocytes and cells with elongated nuclei-like fibroblasts. These cells lie in the adventitial sheath, but a peculiar and characteristic feature is that there is also a definite cellular accumulation in the nervous tissue outside the adventitia. The condition is characterized by an acute onset with headache, vomiting, fever and drowsiness. These symptoms appear about the tenth day on the average. Retention of urine and constipation are usual accompaniments and there may be convulsions. Usually there is some degree of paralysis of the lower extremities, up to complete flaccid paralysis. Reflexes are absent. The duration is usually about eighteen days and about 50% of patients get well. Recovery is complete and there is no residual disability.

Treatment of Empyema in Children.

M. VARGAS (*Archivos Espanolede Pediatria*, June, 1929) treated a child of six years of age who six months before had been operated on by thoracotomy without resection of the rib. He found that the opening had been made very low down, that the drainage tube had pressed against adjacent ribs, causing a fusion of their apposed edges. The diaphragm beneath the wound was so weakened that it became torn during the resection of the ribs which he performed. He considers that this case illustrates some of the dangers of thoracotomy without resection. He makes it his text for a paper on treatment of empyema in children. He gives a history of the factors which have modified his treatment from time to time since 1886. He then outlines his present methods. In serofibrinous pleurisies he aspirates and gives a subcutaneous injection of five cubic centimetres of serum. In purulent interlobar and encysted forms he performs a thoracotomy followed by intrafocal injections of liquids which modify the infection. In free, non-encysted empyemata, having little faith in aspiration of pus, he performs a thoracotomy as soon as possible, preferably under chloroform anæsthesia. In all but children under twelve months he does a resection as well. If the discharge bubbles out freely and if it is mixed with blood at the last, he concludes that the lung has good expansion and resects a portion of only one rib. If it merely dribbles, he resects parts of at least two ribs. He considers the site of election to be the eighth or ninth rib at the posterior axillary line or the angle of the scapula. The pleura is gently irrigated with Dakin's solution, unless there is evidence of a pulmonary fistula. A short drainage tube is inserted. Irrigations with Dakin's solution are made according to certain indications. When the cavity no longer suppurates, the wound is closed. When there is no hope of the cavity closing up, extensive resections are made of the ribs. As soon as the patient has sufficiently recovered, he is recommended climatic treatment and certain exercises.

Asthma.

A. A. OSMAN (*The Lancet*, December 7, 1929, page 1187) has investigated the beneficial effect of sugar upon children suffering from asthma. He records four cases of typical bronchial asthma in children who have been rendered entirely free from attacks over periods of one to two and a half years by the simple addition of sugar to the diet and without any other form of treatment. All the patients were treated at home by the parents and were seen in the out-patient department every fortnight. The treatment consisted of twelve grammes (three drachms) of powdered glucose given in lemonade three times a day between meals. The author is inclined to attribute the beneficial effects to the improvement in general health. Barber and Oriel, however, consider that in these cases there is some hepatic dysfunction and that the sugar exerts its beneficial action on the liver.

Encephalitis.

L. M. MORRIS AND M. MORRIS (*Archives of Pædiatrics*, March, 1930, page 135) discuss the encephalitis which complicates some of the infectious diseases. The lesions of encephalitis in general may be focal or diffuse, with or without involvement of the meninges. Among the possible causes are cocci, bacilli, spirochætes and filtrable viruses. Parenchymatous involvement of the brain takes place by a rather diffuse reaction along the floor of the ventricles and in the brain stem, the cortex remaining relatively intact. The ventricles are only moderately dilated with clear fluid, venous stasis is marked and the chorioid plexuses are swollen and hyperæmic. An attempt is being made, clinically, pathologically and bacteriologically, to subdivide types of acute encephalitis according to ætiology. Symptoms depend largely on the areas of brain involved and meningeal symptoms may be pronounced if the involvement of the meninges is extensive. The authors give a summary of the clinical manifestations of epidemic encephalitis since, as they state, many of these are common to all types. Many sequelæ, however, which are found in the epidemic form, do not occur to the same extent in the other forms. Difficulty may arise in distinguishing clinically between the cerebral form of acute poliomyelitis and encephalitis, but both ætiologically and pathologically these two are quite different. The authors then describe and discuss the occurrence of encephalitis as a complication of epidemic parotitis, measles, vaccinia, varicella, small pox, typhus, rabies—all diseases caused by filtrable viruses. They show that, from a clinical point of view, these conditions are quite dissimilar from a similar group of cases of epidemic encephalitis, particularly in regard to prognosis.

Vulvo-Vaginitis in Children.

K. W. CLAUBERG (*Deutsche Medizinische Wochenschrift*, March 28, 1930) discusses the bacteriology of vulvo-vaginitis in young girls. In a series of 71 infections which clinically resembled gonorrhœa he was unable to isolate the gonococcus. Various Gram-negative diplococci were found, but on culture were not discovered to be gonococci. Usually they were the influenza bacillus or some pleomorphic forms of diplococci. From these results he emphasizes the need for cultural tests in all such infections and not merely reliance on the examination of smears.

The Heart Valves in Acute Rheumatism.

A. F. B. SHAW (*Archives of Disease in Childhood*, August, 1929) reports his findings in a fatal case of rheumatic fever and chorea. He directs his attention particularly to the heart valves and endocardium and to the great vessels arising from the heart. He holds that valvulitis rather than endocarditis is the essential lesion. In the semilunar valves only the base is involved by the fibrosis and Aschoff nodulation, whereas the leafed valves are involved throughout their whole length, probably owing to their varying vascularity. Thus the tricuspid valve is early involved by the embolized virus throughout its entire length and in the pulmonic valve the initial infection can injure only the basal sector. The author produces evidence to show that the frequency of involvement and site of involvement of the various valves also depend to a large extent on the mechanical factor of strain. He emphasizes the fact that valvulitis can be of considerable extent before endocarditis (as indicated by thrombus formation)

begins and therefore no valve can be regarded as free from infection until it has been submitted to microscopical examination.

ORTHOPÆDIC SURGERY.

Tuberculosis of the Spine.

F. H. ALBEE (*Journal of the American Medical Association*, May 10, 1930) discusses his experience with the bone graft operation for tuberculosis of the spine over a period of twenty years and reviews the results obtained in 865 cases. He contends that the graft of living bone promotes ankylosis by stimulating the blood supply where it has been rendered defective by the tuberculous process and in addition increases osteogenic power and provides an immediate mechanical support. He considers that the good results cannot be explained on a basis of immobilization alone. He operates on any patient at any age, provided the surgical risk is good. This depends on skill and rapidity with which the operation was carried out, the time that has been allowed to elapse since the bacteriæmia with its accompanying high temperature has settled down, and various other considerations. He does not consider the presence of multiple lesions to be a contraindication of operation. The presence of sinuses, even when so placed as to encroach on the field of operation, only renders the indication for the operation stronger. When the sinus encroaches on the field of operation the sinus is sealed with a collodion tampon before the operation is begun. The author maintains that even in children advantage should be taken of the speed and safety of the operation to assist ankylosis. As a general rule he uses the massive graft, but where there has been excessive kyphosis he uses several slender grafts tied into a "bundle of reeds" by kangaroo tendon. The patient is kept in bed for five or six weeks and wears a Taylor's spinal brace for from four to six months afterwards. He draws attention to the variations from his original technique and insists that greater care should be observed in following out the details in order to secure good results.

Primary Nerve Lesions in Injuries of the Elbow.

R. WATSON JONES (*The Journal of Bone and Joint Surgery*, January, 1930) describes and classifies the primary nerve lesions in injuries of the elbow and wrist, concluding that primary ulnar palsy in elbow injuries has the same pathogenesis as delayed ulnar palsy, being produced by traction in *cubitus valgus* deformity. Contusion of the nerve is rare. Primary musculo-spiral and median palsies are due to traction in backward displacement and frequently require exploration in supracondylar fractures. Primary ulnar palsies in wrist injuries rarely arise by traction, but sometimes complicate severe displacement of the lower radial epiphysis. Primary median palsy in wrist injuries is almost always due to forward dislocation of the *os lunatum*.

Uses of the Bone Graft.

F. H. ALBEE (*Proceedings of the Royal Society of Medicine*, April, 1930) describes the principles underlying successful plant grafting and maintains that the same principles must be observed to insure success in bone grafting. These are the selection of similar tissues, the maintenance of intimate contact and absolute immobility. He describes various types of grafts, such as the inlay graft which finds its principal use in the treatment of malunited fractures of long bones. He claims that this graft not only throws out callus and ossifies it, but responds to biological demand according to Wolff's law and enlarges and thickens and takes on the structure of the host bone in addition to stimulating function in these sclerosed fragments. This type of graft is also useful for extra-articular arthrodesis of the hip or spine. The inlay graft is used when the bones to which it is applied are vascular and of under-diminished osteogenetic power and are intended to add to or accentuate existing contours in order to overcome some abnormality. The peg graft is most commonly used in ununited fracture of the neck of the femur. The author maintains that the marrow, endosteum and periosteum of the graft must carry the circulation through from the periosteum of the trochanter into the zone of the fracture. The screw graft is made by machine from living autogenous bone in the operating room and is used when the host bone is thin or in some instances of fracture of the patella to insure that the graft will not be pulled from its bed by tension of muscle. It is ideal for use in fresh oblique fractures. The bone muscle lever, used in reconstruction of the hip joint, is actually a process of autogenous grafting resulting in the restoration of the leverage action of the neck of the femur and reestablishment of the function of adduction. Less common uses of bone graft arise in severe cases of scoliosis in the creation of digits and in the treatment of congenital contracted pelvis.

Acute Osteomyelitis of the Fibula.

HAMILTON BAILEY (*The British Journal of Surgery*, April, 1930) states that as far as the treatment of acute osteomyelitis is concerned, the fibula, by virtue of its anatomical and functional peculiarities, stands in a class by itself. It is for the fibula and for the fibula alone that diaphysectomy can be recommended without hesitation. The lower end is divided first and whilst the upper end is being sectioned with the shears, Doyen's raspatory remains *in situ* around the extreme upper end of the bone, protecting the nerve. As soon as the shaft of the fibula has been removed, its bed is swabbed out with a watery solution of flavine and the wound closed by interrupted sutures, except for a glove drain in its lower end. No permanent disability attends the removal of the shaft of the fibula.

Congenital Dislocation of the Hip.

C. H. JAEGER (*Surgery, Gynecology and Obstetrics*, April, 1930) discusses the opinions of various authors indicating the present practice of open reduction of congenital dislocation of the hip. He contends that it is possible to diagnose the condition within a few months of birth and maintains that it is possible to obtain perfect reduction, good function and early use of the limb by means of his "physiological" method of reduction which he claims requires no more than three months. So far he has applied it only to unilateral dislocations. The method consists of the use of a long hip splint of rustless steel composed of two circular bands to fix the pelvis and chest and two lateral bars to support the leg. To the lower ends of the bars is attached a footplate with a leather anklet to maintain the leg in the mid-position between outward and inward rotation. The long outer bar is bent to fit the leg at 45° abduction. With this apparatus in position he obtains gradual reduction of the dislocated head by means of an adjustable pad controlled by a wing screw about 3·75 centimetres (one and a half inches) long, placed directly over the trochanter and pressing downwards and inwards. He maintains that this treatment does not in any way retard the normal development of the child.

Hip Anomalies in Man.

M. JANSEN (*The Journal of Bone and Joint Surgery*, July, 1929) discusses his theories of the changes typical of *coxa vara*, *coxa fracta*, *coxa plana*, *coxa valga*, slipping epiphysis and *malum coxæ*. His contention is that these various conditions, representing malformations at different periods of the life of the head of the femur, are due to the anatomical variations in the shape of the socket of the hip joint. The underlying anatomical variations he refers to as *ischium varum*. In this condition the flattening or widening of the hip socket is present before the widening of the femoral head and it remains stationary for years while *coxa plana* is developing. He considers that the changes commencing with flattening of the hip joint socket are primary to changes of the femoral head and need not be increased by the latter. He discusses the various other theories of the causation of Perthes's disease and claims that internal trauma due in the case of the femur to the disparity between the size of the fœtus and the fœtal envelopes, is responsible for the pathological changes which have been observed in the head of the femur and have been ascribed by various authors to external trauma.

Special Articles on Diagnosis.

Contributed by Request.

I.

CEREBRO-SPINAL SYPHILIS.

IN order that we may be clear on the meaning of this heading, let me say at the outset that I find it convenient to follow those British writers who think of cerebro-spinal syphilis, or syphilis of the central nervous system, as being composed of two main forms named "meningo-vascular" and "central." The "meningo-vascular" form takes in everything due to primary spirochætal invasion of the meninges and blood vessels of the central nervous system, and it is the diagnosis of this form alone that I propose to discuss. The "central form," denoted by the terms parasyphilis, metasyphilis and parenchymatous syphilis, illustrated by general paralysis of the insane, *tabes dorsalis*, and, according to some, optic tabes or atrophy, and carrying the whole riddle of parasyphilis, I shall not touch.

When Oppenheim, as far back as the year 1896, published his well known monograph on syphilitic diseases of the brain, the fact was brought home to all that multiplicity of lesion and in consequence a protean symptomatology was a fundamental character. Now in diagnosis the horde of symptoms may first be divided into two main classes, (*a*) precursory symptoms which are insidious and unobtrusive, and (*b*) final or declared symptoms which are blatantly indicative of a process of destruction.

Precursory Symptoms.

As to precursory symptoms, it often happens that a patient comes presenting suspicious indications and the first question we need an answer to is, whether or not has there been infection with syphilis? Formerly proof of such infection entailed a painful *questionnaire* and a search for signs often unconvincing, but the advent of the Bordet-Wassermann test ended all this and now we simply request the patient to visit a pathologist upon whom we put the onus of probation. And here I need hardly say that in some cases when the blood does not yield a reaction we ask for a test of cerebro-spinal fluid and an examination for pleocytosis and excess of globulin. Next, what are the suspicious indications or precursory symptoms which call for this laboratory investigation?

Pupillary Anomalies and Vertigo.

To begin with, it is an unequivocal fact that the *Spirochæta pallida* has a predilection for tissues in the neighbourhood of the third nerve nucleus. Accordingly, just as *tabes dorsalis* and general paralysis are characterized by abnormal reactions of the pupil, so also in meningo-vascular syphilis, and as an early sign, some inactivity to light or some inequality or some defective centring of the pupils is a most useful diagnostic sign. Of course, similar pupillary anomalies appear in non-syphilitic affections, but so infrequently as to be negligible. A beginning retinitis is another ocular change which examination of the fundi may reveal. Also as another symptom of cranial nerve disturbance vertigo is a frequent early complaint which a Bárány test may prove to be due to disordered function of the internal ear.

Headache.

Headache is a constant early feature and as a rule is both severe and paroxysmal. (The old teaching that the syphilitic headache is specially prone to be nocturnal is not now generally accepted.) If the head pain be constant, instead of paroxysmal, and localized, as well as attended by scalp tenderness, a subjacent gumma may be suspected, and if with this there should happen to be vomiting and papillœdema, obviously confusion with a non-luetic tumour of the brain is a likelihood.

Insomnia.

Insomnia is another early complaint and sleep, when it comes, is disturbed by distressing dreams. Should the insomnia be accompanied by headache and lassitude, as it frequently is, the affection may come to be falsely labelled neurasthenia. Indeed this confusion of syphilis of the nervous system with neurasthenia is very common, as well as very serious, when we think of treatment. It is an error more likely to arise in general than in hospital practice, simply because in hospitals nowadays a Bordet-Wassermann test is almost a matter of routine. And what has just been said concerning neurasthenia applies with almost equal force to hysteria. Any with neurological experience can give instances in which meningo-vascular syphilis has resembled and been mistaken for hysteria. Narcolepsy in idiopathic form is another affection not to be too confidently diagnosed, because it is a recognized failing of the cerebral syphilitic to fall asleep abruptly and at odd times during the day.

Affection of Spinal Roots.

Since the spirochæte of syphilis has a liking for the spinal as well as the cerebral meninges, it should never be forgotten that some affection of spinal nerve roots is an early occurrence. Spirochætal invasion of the posterior roots is suggested by vague pains arising in any part of the body, but particularly the trunk. And careful examination may disclose areas of tenderness and perhaps sensory loss, having a root distribution. It is in cases of this kind that a routine neurological examination may prevent the erroneous diagnosis of pleurisy, gall stones, appendicitis and so forth. As to the anterior spinal roots, though early affection of these is infrequent, a local muscular paralysis and wasting may appear as an indication and as rapidly disappear under appropriate treatment. Also indicative of spinal affection and perhaps accompanied by some signs of myelitis, there may be disturbance of bladder function, consisting of retention or incontinence of urine, possibly followed by cystitis. Such disorder may be the patient's first reason for consulting his doctor.

Mental Changes.

Lastly, it is important to remember that the activity of meningo-vascular syphilis is productive of mental disorder which is both characteristic and may arise as one of the first phenomena. Very frequently personal complaint is made of loss of concentration and uncertainty of memory, while friends observe emotional weakness, change of disposition and a general falling off in capacity. At times this disorder advances to such degree as to justify being called a state of dementia, the amnesia in particular being as profound as in Korsakow's psychosis of chronic alcoholism. Again, in some cases an alarming epileptiform seizure occurs and may be the first warning that anything is amiss. In view of the foregoing, it is not unreasonable to contend, as some do, that cases of this kind come to be diagnosed as general paralysis of the insane and consequently figures dealing with the curability of general paralysis by modern methods come to be vitiated.

From these remarks on premonitory symptoms it may be granted that although some of the features of incipient meningo-vascular syphilis may be disclosed only by searching examination of the nervous system, on the whole the clinical picture is fairly distinct. It must also be plain that diagnosis at this stage is all important, because by prompt attack with appropriate treatment the patient may be saved from the development of those gross lesions and fulminant signs which next proclaim themselves.

Final or Fulminant Symptoms.

It is when we come to declared meningo-vascular syphilis that we find the manifestations to be protean and small wonder that this is so when we consider that while syphilis is specially prone to attack parts related to meninges, there is actually no part of the central nervous system which it spares. In this circumstance and since one patient usually offers many signs or symptoms, it only confuses to think of types of affection. It is impossible to

divide meningo-vascular syphilis into clearly cut forms, as has been done with central syphilis. Syphilitic meningitis is never pure; even Erb's "syphilitic spinal paralysis" is not acceptable as a special disease of the spinal cord. It is certainly more convenient from the point of view of diagnosis to group signs and symptoms in accordance with the anatomical distribution of the lesions. Accordingly to meet the purposes of this *résumé* they will be considered under the headings: (i) Affections of cranial nerves, (ii) purely cerebral affections and (iii) affections of the spinal cord.

Affections of Cranial Nerves.

Beginning with affections of the cranial nerves, it is universally accepted that disordered function of the cranial nerves is the commonest indication of meningo-vascular syphilis, the reason being that the spirochæte is specially prone to lodge in the basal meninges. The disturbance of function in these nerves may be on one or both sides and in every conceivable combination. Oculo-motor paralyses of all kinds, from a simple turning of one eye to bilateral external ophthalmoplegia, paralysis of the face, tongue, palate, vocal cord or sterno-mastoid, subtle dissociations in vestibular tests, cardiac and respiratory disturbances instanced by the cyanosis and bradycardia of so-called "medullary fits," all these occur, often mixed, and give an idea of the variety of affection. In the matter of diagnosis it is to be kept in mind that some of these affections are rare and encountered almost only in syphilitics; that the combinations may be bizarre and very different from those of non-specific diseases, such as pontine and medullary tumours; that the cranial nerve paralysis may be associated with crossed paralysis of limbs *et cetera* (*vide* a number of uncommon syndromes); and that usually there is concomitant affection of spinal meninges and roots. This last serves as one distinguishing feature from epidemic encephalitis which alone of all diseases of the nervous system may occasion a medley of cranial nerve disturbances at all resembling those of malignant basal syphilis, albeit some mention tuberculous meningitis as a possible source of confusion.

Purely Cerebral Affections.

Among signs of the purely cerebral forms of meningo-vascular syphilis an attack of hemiplegia is the most widely recognized and may be the opening major sign. Suspicion of syphilis should be aroused by the relative youth of the patient, and independently of the Bordet-Wassermann test the discovery of minor syphilitic indications may settle the diagnosis. Since reaction to treatment is also a distinguishing feature, the importance of early differentiation is evident. Although hemiplegia is the commonest phenomenon, practically every clinical manifestation of localized brain lesion may be represented in these subjects. Also, as Oppenheim showed when he described what he called "basal gummatous meningitis," there may be multiple gross lesions leading even to almost total eclipse of brain function. Any with experience of such cases will realize their tragic nature; fortunately they are uncommon and perhaps less common than in Oppenheim's day. These gross forms of disorder are chiefly due to endarteritic closure of main vessels. Another form of affection which some have called "syphilitic encephalitis," may be due to widespread meningitis and closure of smaller vessels. Such affection accounts for profound hebetude, loss of memory or a mental state which may resemble either *dementia præcox* or *dementia paralytica*, and be difficult of diagnosis. Again, persons with some constitutional paranoid or schizoid disposition may have frank paranoia or schizophrenia (*dementia præcox*) precipitated or determined by the influence of the spirochæte on brain cortex (Plaut, Wimmer). Syphilis may also produce an epilepsy like idiopathic epilepsy and even more refractory to treatment. But such cases are rare; besides it is always difficult to be sure that the epilepsy did not precede the syphilis. We must not label an epilepsy or a psychosis as syphilitic simply because the patient happens to be syphilitic. Indeed, not only here, but as regards other affections, perhaps the old warning of Virchow not to neglect the possibility that a syphilitic individual may suffer from an affection of non-syphilitic origin is too often forgotten.

Affections of the Spinal Cord.

Turning to the spinal cord, as Nonne and others have shown, the syphilitic subject at any time after infection may be attacked with degrees of paraplegia, spasticity and so on, having all the characters of a partial or complete transverse myelitis, and the essential lesion is syphilitic meningitis *plus* vascular changes. But in addition to forms of affection which resemble myelitis, there are others to confuse diagnosis. Thus it is quite common to meet with examples resembling disseminated sclerosis and lateral sclerosis, particularly the former, and, though uncommon, to meet with resemblances to crossed paralysis (Brown Sequard), acute anterior poliomyelitis, progressive muscular atrophy, postero-lateral combined degeneration, syringomyelia and *tabes dorsalis* (syphilitic pseudo tabes). These all have to be remembered, indeed, differentiation is all important. For example, what can be more gratifying than to be able by treatment to arrest the creep of the paralysis in one presenting the appearances of progressive muscular atrophy. But here it may be noted that according to some observers there are two forms of syphilitic progressive muscular atrophy, one "meningo-vascular" and tractable, the other "central" and intractable. In the case of all these syphilitic spinal affections correct diagnosis is usually enabled by careful examination. It is a help to know that some symptoms may be present in the specific sufferer which are always absent in the non-specific or characters of the non-specific may be wanting. It is also useful to remember that when the cerebro-spinal fluid in these cases comes to be tested it will be found that the Bordet-Wassermann reaction is extremely positive, as was first observed by Sir Henry Head.

Finally, as regards the incidence of meningo-vascular syphilis relative to infection, it is a mistake to suppose that we have to wait for the tertiary period. Sir Frederick Mott's statement that there is no period of safety has been abundantly proved, or to use Sir Henry Head's words: "Two patients may be attacked for the first time with identical nervous manifestations; yet the one is obviously in the secondary stage, three months after infection, whilst the other was infected twenty-five years before."

ALFRED W. CAMPBELL, M.D.,
Consulting Neurologist, Royal Alexandra Hospital, The Coast Hospital and Prince of Wales Hospital, Sydney.

British Medical Association News.

SCIENTIFIC.

A MEETING OF THE WESTERN AUSTRALIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the Lyceum Theatre, Mount Lawley, on May 22, 1930, DR. H. B. GILL, the President, in the chair.

Australasian Medical Congress (British Medical Association).

On the motion of DR. D. M. MCWHAE, seconded by DR. T. L. ANDERSON, Dr. D. D. Paton was unanimously nominated as President for the Fourth Session of the Australasian Medical Congress (British Medical Association).

On the motion of DR. D. M. MCWHAE, seconded by DR. T. L. ANDERSON, all the members of the Western Australian Branch were appointed a general committee of congress. The appointment of honorary secretaries and of an honorary treasurer was deferred.

Dr. McWhae said that it was customary to hold a staff ride under the direction of the Section of Naval, Military and Air Medicine and Surgery at each session of Congress.

He announced that a military staff ride would be held on June 1, 1930, as a preliminary and possibly as a pattern for the staff ride to be held at Congress. He invited all members of the Branch to be present.

DR. D. D. PATON expressed his thanks for the confidence which the members of the Branch had reposed in him in approving of his nomination as President of Congress. He laid stress on the need for cooperation and support from all the members. Without such support, not only would the members of the Executive Committee be overworked, but the smooth running of Congress would be impossible.

The Harvey Film.

The Harvey cinematograph film was shown.

DR. A. WEBSTER, in introducing the film, said that if it were true that good wine needed no bush, it was also true that a good picture needed no prologue. The responsibility for his speaking belonged to the Secretary of the Branch.

When a great discovery, such as that of the circulation of the blood, had been registered, it was not inappropriate to inquire what the circumstances were which led up to it. In the case of Harvey the answer was clear—there were four or five links in a chain of circumstances, extending over a period of fifteen years in Harvey's life, preceding the discovery of the circulation which indicated the path. Harvey was born in the year 1578 and at the age of ten he had gone to the King's School at Canterbury where he acquired a solid grounding in the Greek and Latin languages; this had not only enabled him to read and understand what Aristotle and Galen had taught, but it had also revealed to him the nature of the problem which he was destined to solve. At the same school, in the second place, he had gained a scholarship the terms of which directed that he, the scholar, should devote himself to the study, in the first place, of those subjects which led up to medicine and, secondly, to the study of those subjects which constituted medicine itself.

Accordingly, in the year 1593, when he was fifteen years of age, Harvey had gone to Cambridge and entered at Caius College. That college, as its name implied, had been founded by John Caius who was one of the foremost anatomists in England before Harvey's time. Caius had been at Padua and he had not only studied anatomy under Vesalius, the greatest anatomist of his age, but he had lived in the same house with Vesalius; he had taught anatomy at Padua and subsequently he lectured on anatomy in London. It was not surprising, therefore, that Harvey should follow the footsteps of the founder of his college to Padua.

Harvey had gone to Padua probably in the year 1600 and it was here that they came upon the fourth link in the chain of circumstances; this link was constituted by Harvey's association with Fabricius.

Fabricius had described the valves in the veins in the year 1574, just four years before Harvey was born. In Harvey's great work "*De Motu Cordis*," as it was briefly termed, there were only two plates of two figures each and each of these plates represented the position of the valves in the veins of the human forearm.

In the year 1602 Harvey had taken the degree of doctor of medicine at Padua and returned to London where he commenced those experiments upon what he termed "The Movement of the Heart and Blood in Animals."

These experiments had been reconstructed two years before by Sir Thomas Lewis and Dr. Dale in London, and having been reproduced in the form of a film would be projected on the screen that evening.

Dr. Webster said in conclusion that he had seen this film and was therefore not anticipating in asking to be allowed to join with them in thanking Dr. Rowden White, of Melbourne, for affording them the unique opportunity of viewing so remarkable a film.

The Canti Film.

The Canti cinematograph film was shown. DR. L. E. LE SOUEF said that when he was privileged to view this remarkable and important film at Saint Bartholomew's Hospital, London, some eighteen months previously the conditions had been ideal, as not only did a large and enthusiastic medical audience see a cinematograph film which was unique, but they had also heard its creator, Dr. Canti himself, describe the technical difficulties he had had to overcome before such a work could reach fruition, and later, whilst the film was in progress, demonstrate points of interest to an eager and appreciative audience.

That the members of the Western Australian Branch should have the opportunity of seeing this film which had achieved for itself and its creator an enviable position on the scroll of medical fame, was entirely due to the efforts of Dr. Julian Smith, of Melbourne. This gentleman who was well known personally to most of them, not only as an esteemed colleague, but as a friend, was deserving of their greatest gratitude, for he had seen fit, despite personal inconvenience, to bring before them in Australia material of great importance and material which had to be seen to be appreciated—the product of much patient research in England.

Technically the difficulties had been twofold. In the first place the apparatus had had to be evolved and, secondly, a suitable medium for the tissue growth had been necessary, as in the dark ground illumination shown in the third reel the slightest deviation from a truly homogeneous medium was found to detract from the clarity of the photographs. That both these difficult problems were overcome would be obvious.

Exposures taken at intervals of up to sixty seconds and extending over periods of days led to a speeding up of 960 times with the cinematograph running at the normal rate. The cell movements as photographed could be studied with deliberation and as a practical application, the effects of radium on growing chick periosteum and on Jensen's rat sarcoma, growing as tissue cultures, had been studied in this film.

Dr. Le Soeuf said that before the release of the film he wished to draw the attention of members more particularly to certain points. The irradiation was unscreened and intense and so contained also β rays. The effect on the chick's periosteum was more marked on the wandering cells, whereas the fibroblasts showed little change, few showing the disintegration undergone by the wandering cells. The effect on the rat sarcoma was marked in the case of both wandering and fibroblastic cells, the time taken being somewhat similar to that taken in the destruction of the wandering cells of the chick's periosteum. Thus one could observe the selective action on the malignant cells and, furthermore, the action on the wandering cells of normal tissue. Throughout, all processes of mitosis would be seen to undergo arrest on irradiation.

NOMINATIONS AND ELECTIONS.

THE undermentioned have been elected members of the Queensland Branch of the British Medical Association:

Castellano, Francesco, M.D., 1922 (Univ. Naples), Ingham, North Queensland.

Hoban, Maxwell, M.B., B.S., 1929 (Univ. Melbourne), Mater Misericordiæ Public Hospital, South Brisbane, Queensland.

O'Sullivan, Emil John, M.B., Ch.M., 1926 (Univ. Sydney), Archer Street, Toowong, Brisbane, Queensland.

Post-Graduate Work.

LECTURES IN MELBOURNE.

ATTENTION is again drawn to the lectures which will be delivered in Melbourne under the auspices of the Melbourne Permanent Committee for Post-Graduate Work by Professor Evarts Graham, Professor of Surgery in the Washington School of Medicine, St. Louis, United States of America. The syllabus of lectures is as follows:

Thursday, July 17: "The Significance of Changed Intrapleural Pressures to the Problems of Empyema and other Thoracic Diseases."
Friday, July 18: "Pulmonary Suppuration."
Monday, July 21: "Surgical Treatment of Pulmonary Tuberculosis."
Tuesday, July 22: "Physiology and Pathology of the Gall Bladder."
Thursday, July 24: "Cholecystography."
Friday, July 25: "The Clinical Significance of Tests of Hepatic Excretion."

The lectures will be delivered at the Medical Society Hall, Albert Street, East Melbourne, at 8.30 o'clock p.m. The fee for the course is four guineas.

ANNUAL REFRESHER COURSE IN MELBOURNE.

The annual refresher course, arranged by the Melbourne Permanent Committee for Post-Graduate Work, will be held, at previously announced, from July 14 to 26, 1930. The fee for the course is three guineas. The syllabus was published in the issue of June 21, 1930, at page 826.

LECTURES IN SYDNEY.

THE Post-Graduate Committee of the New South Wales Branch of the British Medical Association announces that through the courtesy of the Melbourne Permanent Committee for Post-Graduate Work arrangements have been made for Professor Evarts Graham, Professor of Surgery of Washington University, United States of America, to lecture in Sydney towards the end of July, 1930. Further particulars will be announced at a later date.

Obituary.

ARTHUR STYLES VALLACK.

THE death of Dr. Arthur Styles Vallack, recorded in the issue of June 14, 1930, has left a serious gap in the ranks of the medical profession in New South Wales. Brilliant as a student, successful in sport and later faithful in practice, he was so free from mercenary and selfish quality that it was a refreshment to come into contact with him.

The son of the late R. G. Vallack, sometime managing director of William Gardiner and Company, Arthur Styles Vallack was born at Sydney, close to the site of the present Central Railway Station. His early youth was spent at Homebush and he went to school at Newington College. Here he distinguished himself; he did well in science and represented his school in both cricket and football. He passed his senior public examination in 1888, taking the medal in chemistry. He matriculated in 1889 and entered the University of Sydney as an undergraduate in the Faculty of Arts. In the first year examination he gained honours in chemistry and was second on the pass list in English, gaining the Levey Scholarship. In those days it was usual for many students to spend a year in the Faculty of Arts before they embarked on the study of medicine. Undoubtedly Vallack would have distinguished himself had he given his life to letters. His adventures in literature in later years bear the stamp of originality and culture.

Having chosen medicine as his career, Vallack soon made his mark. He passed his first professional examination in 1890, top of his year, winning the Renwick Scholarship and gaining first class honours in every subject. At his second professional examination in 1892 he passed with credit, being placed first in anatomy, first (*proxime accessit*) in *materia medica* and second in physiology and pathology. He graduated in 1893 and was bracketed equal with Grafton Elliot Smith. At the University he took his place in the playing fields; he won his blue for cricket, played with the "A" team in football and was prominent in athletics. He was a member of the Cricket Committee, Treasurer and later President of the University Medical Society, Vice-President of the University Undergraduates' Association and co-editor of *Hermes*. After graduation he became Resident Medical Officer at the Royal Prince Alfred Hospital and later Senior Resident Medical Officer. He then went to the United Kingdom and became a Licentiate in Midwifery of Rotunda, Ireland.

After his return to Australia Vallack took up practice at Bowral, New South Wales. His stay in this country town was marked by thoroughness and attention to detail and a desire to advance knowledge. His partnership with Dr. Throsby was a happy one, as may be gathered from the latter's appreciation of his friend. Shortly after starting practice in Bowral, Vallack married Blanche, daughter of the late Reverend R. Mackinnon. His wife's devotion and cooperation was no small factor in his success, for he was successful—his practice extended from Picton in the north to Goulburn in the south. He was honorary surgeon to the Berrima District Hospital. His first operation in Bowral was a hysterectomy, performed on a kitchen table. When he left Bowral the hospital could boast a modern operating theatre and equipment. It was at this time that he carried out his observations and write his book, "Asepsis," published by Baillière, Tindall and Cox. Dr. Throsby has given an excellent description of Vallack's work on asepsis. During his sojourn at Bowral he contributed several articles to the *Australasian Medical Gazette*. He also played a prominent part in the activities of the town, being conductor of the Music Club, captain of the Cricket Club, captain of the Golf Club and municipal councillor. He was surgeon to the Berrima Gaol.

In 1911 Vallack came to North Sydney where he went into partnership with his brother-in-law, Dr. R. R. S. Mackinnon. He was appointed Honorary Assistant Surgeon to the Royal Prince Alfred Hospital. In 1914 he was appointed full surgeon to the Mater Misericordiæ Hospital, North Sydney, and occupied this position till his death. He resigned his position at the Royal Prince Alfred Hospital in 1918 owing to pressure of other work. During the war years Vallack held the rank of captain in the Australian Army Medical Corps and was given home service duties to perform. From 1920 onwards he gave much time to literature and published a play, "One Year," which was produced and received favourable criticism. Towards the end of his life he made tennis his recreation.

Vallack achieved much in his lifetime. He earned and held the respect and admiration of his *confrères* and many of them had for him an affectionate regard. He would be lavish with his help without thinking of personal gain or aggrandizement. His wife died about three years ago. To his son, Dr. Richard Vallack, the sympathy of the medical profession is extended.

Dr. Herbert Throsby writes:

The sudden and untimely death of A. S. Vallack came as a great shock to his many friends and admirers and his numerous patients will always remember him with affection and gratitude. Gifted with a wonderfully keen and quick brain and with the critical faculty highly developed, it was little wonder he was so highly thought of in the profession in New South Wales.

At school and Sydney University he was naturally a brilliant scholar. In his final M.B. examination he was bracketed equal with the great Elliot Smith—a really great achievement in view of the latter's present status in the scientific world. Going on to the Royal Prince Alfred Hospital as house surgeon and afterwards assistant medical superintendent, he laid that basis of scientific surgery for which he was afterwards so well known. His remarkable keenness for all branches of medicine and surgery and his wide and critical reading made him noticed even among such brilliant contemporaries as Sawkins, Maitland and Elliot Smith. After leaving the Royal Prince Alfred Hospital he went to Europe for post-graduate study and did the obstetric course at the Rotunda Hospital where he was greatly impressed by the teaching of Sir

William Smellie who at that time was the leader of the new aseptic midwifery.

The writer well remembers his return to Sydney in the early 'nineties, keener than ever and fairly bubbling over with all he had seen and learnt. He gave a lecture at the Royal Prince Alfred Hospital before the University Medical Society on "Aseptic Surgery" and together with Hinder was the first to emphasize by preaching day in and out the importance of the work of Schimmelbusch on aseptic surgery as against the antiseptic surgery of Lister. In those days surgical wounds did not heal as they do now and there were many tedious and dangerous suppurations, even in the best hands at the large teaching hospitals. Vallack fulminated against much of the antiseptic ritual and was for ever thinking out new methods of skin cleansing for the surgeon and the patient. For, like Hinder, his scientific mind soon recognized that the skin of the hands of the surgeon or nurse was the main carrier of infection in wounds in spite of every attempt at cleansing by soap and antiseptic, and one of his slogans was: "Never soil your hands, if possible, with septic material, because it takes days, and possibly weeks, before natural desquamation got rid of virulent germs in the epidermis."

Years afterwards the writer was associated in partnership with Vallack in the country and one remembers only too well our hopeless experiments in skin disinfection—how the broth inoculated with skin scrapings always became cloudy in spite of all kinds of methods and antiseptics.

The advent of the rubber glove for surgical operations and midwifery he hailed with delight, somewhat dampened, however, by the loss of touch inevitable in the first rather crude gloves. It was then he wrote his book on "Asepsis," so well and favourably reviewed at the time. His original work on the sterilization of catgut by heating it in creosote and the designing of the necessary apparatus was all done while he was a country practitioner.

To be a scientific surgeon in the best sense of the word was always Vallack's one aim in life. His dexterity was considerable and his technique always of the best. Yet his thought was always for the ultimate good of the patient and not whether he could perform a brilliant piece of operative work and perhaps leave the patient very little the better for it. He was thus thoughtful and careful in all his work and, in this respect, a great example for younger men to follow.

But Vallack was not only a keen worker at his profession. He was also the keenest of sports and excelled at cricket, golf and tennis and his intense love of music gave him many a happy hour. He was a voracious reader, not only of medical literature, but in all branches of science and philosophy and general literature. Many of his friends will remember his illuminating talks and discussions on many subjects, from the latest novel to the philosophy of Kant or Herbert Spencer. In later life he was much interested in the modern drama and he has left behind at least two completed plays which may yet be seen on the stage.

One regrets profoundly that his life ended just at the time when his experience had ripened and when his friends looked that he might yet produce something remarkable in literature. He was a loyal friend and a most devoted husband and father and his only son who succeeds him in his practice, will have the deepest sympathy of his professional colleagues and his many patients and friends.

Dr. Gilbert G. Bradley writes:

As one of Dr. Vallack's old house surgeons, may I be permitted to add my tribute to the memory of one who was held in high affection and esteem by all with whom he came in contact?

My association with him dated from 1922 when, as his resident at the Mater Misericordiæ Hospital, I first began to realize how vast was his knowledge and how generous his outlook. There was no subject, professional or otherwise, upon which he could not speak authoritatively.

Essentially a surgeon, he was in truth a specialist in every branch of medicine, with an unsurpassed faculty for imparting his knowledge. He was a voracious reader and I do not think there ever was a book published that he had not read and could not discuss.

He had numerous little personal traits that endeared him to us of the "Mater" staff. His habit of talking throughout the whole course of an operation was well known and many a helpful point was gleaned in this way by successive groups of residents. Every nurse was "lassie" and every resident or junior honorary "sonny" or "laddie" to him. Once, when called in in consultation to see an old lady of over sixty, I remember his addressing her as "lassie," much to her delight. Firm he could be when necessity arose, but his firmness was always tempered with kindness and in his rare occasions of anger he was always notoriously just. "Old Tosh," as he was affectionately called, had a peculiar habit of sitting for minutes, thinking, before alighting from his car, both at hospital and on his rounds. Sometimes the subject of his ruminations would be confided to us and it was always some problem of science or economics or some debatable point in art or literature that had been exercising his brain. He had one pet aversion—communism and all that it means—and one pet surgical fad—the non-existence of chronic inflammatory lesions of the appendix. The latter naturally originated many lively discussions with his colleagues. With all his knowledge he would sometimes appear almost distressed at the incompleteness of human knowledge. An inveterate seeker after truth, he had an acute realization of how far knowledge has yet to go to attain it. He was fond of asking how our profession could ever boast of its knowledge when it was not even able to explain why a measles rash should first appear always on the forehead and face, a scarlet fever rash on the chest and so on.

His surgical ability rivalled his surgical knowledge. Gynæcology he always regarded as "surgery made easy" and did not hesitate to say so. Fractures he loved.

On the tennis court, even in his latter years, he was a most formidable opponent both in doubles and singles. Many men of half his years went down before his superior technique.

"Old Tosh" is gone! But to us who knew him and loved him, there remain a host of delightful associations to perpetuate the memory of one to whom some of us owe so much and about whom no one ever heard a harsh word spoken.

Hospitals.

ROYAL ALEXANDRA HOSPITAL FOR CHILDREN.

THE CAUSE OF DEATH IN DIABETIC CHILDREN.

DR. WILFRED EVANS has forwarded an analysis of the histories of diabetic children who were inmates of the Royal Alexandra Hospital for Children, Sydney, during the years 1927, 1928 and 1929.

The analysis reveals that the death rate in these children is remarkably high and is in the main due to certain well defined causes. Of twenty-nine patients who were in-patients during these years and whose later history it has been possible to trace, fourteen only are living and fifteen are dead. It has not been possible to trace four others.

The mortality rate has thus been slightly in excess of 50% during a comparatively short period and an analysis of the causes leading up to this fatal issue furnishes some interesting figures. Frank coma claimed the greatest number of victims—eight in all and roughly 50% of the deaths. Most of these children were living in the country districts and as a rule they progressed well for a time after leaving hospital, but eventually difficulty arose in completely controlling the disease and the patients drifted into coma. In general the impression derived from the hospital records and information supplied later by the parents was that the best results were obtained in those

children who were given a comparatively liberal carbohydrate diet and sufficient "Insulin" to keep them sugar-free. The most important factors of all, however, appeared to be the standard of intelligence and degree of cooperation of both mother and child.

An interesting point noted in two of the patients admitted to hospital suffering from coma was the presence of almost complete anuria. This is held by Dr. Evans to indicate the necessity of freely administering fluids, intravenously if possible, in severe cases of coma, because such children are not only unable to take fluid by mouth, but are as a rule also vomiting and water deprivation must be a very serious factor in their condition. This point has been stressed by recent writers on the subject.

Of the remaining seven patients who died, one developed coma and died after operative treatment and the remaining six, or 40%, of the total deaths were the direct result of an acute febrile disease. Pneumonia accounted for three deaths, diphtheria one, measles one and scarlet fever one. Dr. Evans points out that these diseases form the second important cause of death in the young diabetics of this series and the treatment of such conditions requires the greatest care. He goes on to state that the dictum of the von Pirquet Clinic is that every diabetic child should be given "Insulin" and not less than sixty grammes of carbohydrate daily, because under such treatment they are better able to withstand the infectious diseases and the tendency to develop acidosis and coma. Further, if any infectious disease does supervene, the calorific value of the diet should immediately be reduced chiefly by the complete elimination of fats, but the dose of "Insulin" should remain at its previous level.

The chief endeavours in combating the high death rate in diabetic children should, then, be spent in more rigorous education and closer cooperation with both mothers and children and greater care in combating the acute febrile diseases of childhood.

Correspondence.

DIATHERMY OF TONSILS.

SIR: In THE MEDICAL JOURNAL OF AUSTRALIA dated June 21, 1930, there appeared two letters dealing with diathermy of tonsils, one written by Dr. Watkins, of Newcastle, and the other by Dr. Culpin, of Brisbane, and one could not help contrasting the courteous and thoughtful letter of Dr. Watkins with the "buffoonery" of Dr. Culpin. No one is more ready than I am to welcome "constructive" criticism in regard to modern methods of treatment, but, instead of offering some really constructive criticism, like Dr. Watkins, Dr. Culpin's extraordinary effusion was merely offensive and utterly worthless as a serious contribution to the solution of the tonsil problem.

It is well known, of course, that when a man has a poor case to defend and the evidence is going against him, he is prone to abuse the other fellow or to attempt to heap ridicule upon him, but I think any unbiased reader will agree that in this case Dr. Culpin has only succeeded in bringing ridicule upon himself. It is notoriously difficult for "an old dog to learn new tricks" and one can appreciate the point of view of those senior men like Dr. Culpin who have spent many years in perfecting themselves in the technique of surgical tonsillectomy and their reluctance to abandon it in favour of a new method such as diathermy. However, it is from the younger generation of progressive surgeons who are taking up diathermy and radium treatment with enthusiasm, that surgical tonsillectomy will receive its death blow.

It may be of interest to Dr. Culpin to learn that, although the removal of tonsils by diathermy has only come into prominence in Australia during the past two years, it has been a well recognized procedure both in Europe and America for many years past and Professor Georges Portmann, of Bordeaux, one of the most eminent throat specialists in France, has been removing tonsils by diathermy with splendid success since 1913 and has long ago abandoned surgical tonsillectomy in favour of this newer and better method. It was from Professor Portmann in 1925 that Dillinger learnt the technique that I employed in the removal of my own tonsils, as described in my letter to the Journal of June 7 and which Dr. Culpin was pleased to refer to as "comic opera." I am sure that Professor Portmann will feel highly complimented when he receives his next number of THE MEDICAL JOURNAL OF AUSTRALIA and reads Dr. Culpin's amazing letter on the diathermy of tonsils.

In conclusion I should like to remind Dr. Culpin that in his "elephantine" attempt to be "funny" he quite forgot to answer even the first of my two questions, *viz.*: "How many of the critics of diathermy would have the courage to remove their own tonsils either with a guillotine or a blunt or sharp dissector?" and I would now ask him to kindly answer this question before indulging in any further "destructive" criticism of the diathermy method of removing tonsils.

If Dr. Culpin accepts the challenge and proceeds to enucleate his own tonsils surgically, I am quite prepared to allow him a course of calcium lactate to shorten his "coagulation time," a preliminary hypo of morphia and atropine to relieve anxiety and, if he feels that painting his tonsils with twenty minims of a 10% solution of cocaine would not give him sufficient anæsthesia, he is quite at liberty to inject a drachm or two of "Novocain" and adrenalin solution into each tonsil area. I am also prepared to allow him the services of a "senior" nurse to give him moral support and do any "mopping" that may be necessary and a theatre sister to stand by with a plentiful supply of "Hæmostatic serum," pituitrin and strychnine to combat hæmorrhage and shock!

Yours, etc.,

A. J. CAHILL.

Sydney Buildings,
City, Canberra, F.C.T.
June 23, 1930.

SIR: In regard to the paper of Dr. A. J. Cahill, of Canberra, in which he graphically described his bold removal of his own tonsils by diathermy operated by himself, I would like to say that in my opinion it is a most enlightening contribution to the subject which has been agitating a number of experts for some time past. So far from being sneered at as "comic opera," I consider that Dr. Cahill's courageous autodiathermy is to be commended as a valuable experiment and he should be warmly congratulated on his enterprise and intrepidity.

Yours, etc.,

T. J. HENRY, F.R.C.S. (Edin.).

27, Fairlight Crescent,
Manly, New South Wales.
June 26, 1930.

A PROTEST.

SIR: May I have a piece of your valuable space to record a protest against an advertisement in your issue of 31st May last, wherein applications are invited for the position of Medical Officer of Health at Bendigo at the ridiculously low salary of £750 *per annum*?

Were this a commencing salary for a junior medical man of ordinary competence and skill, there would be little cause for complaint, but the list of qualifications indicates that an experienced specialist is required.

Is it not time that the British Medical Association in Australia took effective action to insure that reasonably adequate salaries are paid to the occupants of such positions as this?

Yours, etc.,

H. HASTINGS WILLIS,
Honorary Secretary,
Public Medical Officers' Association
of New South Wales.

Sydney, New South Wales.
June 25, 1930.

Proceedings of the Australian Medical Boards.

VICTORIA.

THE undermentioned has been registered under the provisions of Part I of the *Medical Act*, 1928, of Victoria, as a duly qualified medical practitioner:

Tonkin, William Richards, M.B., B.S., 1921 (Univ. Adelaide), Coleraine, Victoria.

For additional registration:

Price, Eric Evan, M.D., 1930 (Univ. Melbourne).

Books Received.

THE DIAGNOSIS AND TREATMENT OF HEART DISEASE: PRACTICAL POINTS FOR STUDENTS AND PRACTITIONERS, by E. M. Brockbank, M.D., F.R.C.P.; 1930. London: H. K. Lewis and Company Limited. Crown 8vo., pp. 256, with illustrations. Price: 7s. 6d. net.

THE MEDICAL ANNUAL, A YEAR BOOK OF TREATMENT AND PRACTITIONER'S INDEX, Forty-eighth Year: 1930. Bristol: John Wright and Sons Limited; London: Simpkin Marshall Limited. Demy 8vo., pp. 752, with illustrations. Price: 20s. net.

SOME ASPECTS OF THE CANCER PROBLEM: AN ACCOUNT OF RESEARCHES INTO THE NATURE AND CONTROL OF MALIGNANT DISEASE COMMENCED IN THE UNIVERSITY OF LIVERPOOL IN 1905 AND CONTINUED BY THE LIVERPOOL MEDICAL RESEARCH ORGANIZATION (FORMERLY THE LIVERPOOL CANCER COMMITTEE), TOGETHER WITH SOME OF THE SCIENTIFIC PAPERS THAT HAVE BEEN PUBLISHED, edited by W. Blair Bell, B.S., M.D., F.R.C.S., Hon. F.A.C.S.; 1930. Sydney: Angus and Robertson; London: Baillière, Tindall and Cox. Imp. 8vo., pp. 557, with illustrations. Price: 63s. net.

DISEASES OF WOMEN, by Ten Teachers, edited by Comyns Berkeley, H. Russell Andrews and J. S. Fairbairn, Fourth Edition; 1930. London: Edward Arnold and Company. Royal 8vo., pp. 570, with illustrations. Price: 18s. net.

Diary for the Month.

JULY 8.—New South Wales Branch, B.M.A.: Ethics Committee.
JULY 8.—New South Wales Branch, B.M.A.: Post-Graduate Committee.
JULY 10.—Victorian Branch, B.M.A.: Council.
JULY 10.—Queensland Branch, B.M.A.: Surgical Section.
JULY 10.—New South Wales Branch, B.M.A.: Clinical Meeting.
JULY 11.—Queensland Branch, B.M.A.: Council.
JULY 22.—New South Wales Branch, B.M.A.: Medical Politics Committee.
JULY 22.—Queensland Branch, B.M.A.: Obstetrical Section.
JULY 23.—Victorian Branch, B.M.A.: Council.
JULY 25.—Queensland Branch, B.M.A.: Council.
JULY 31.—New South Wales Branch, B.M.A.: Branch.
JULY 31.—South Australian Branch, B.M.A.: Branch.
JULY 15.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Medical Appointments Vacant, etc.

FOR announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," page xvi.

ALFRED HOSPITAL, PRAHRAN, MELBOURNE, VICTORIA: Pathologist.
DEPARTMENT OF INSPECTOR-GENERAL OF HOSPITALS, SOUTH AUSTRALIA: Resident Medical Officer.
KINGAROY DISTRICT HOSPITAL, QUEENSLAND: Medical Officer.
LEWISHAM HOSPITAL, SYDNEY, NEW SOUTH WALES: Honorary Radiologist.
NEWCASTLE HOSPITAL, NEWCASTLE, NEW SOUTH WALES: Junior Resident Medical Officer.
SWAN HILL DISTRICT HOSPITAL, VICTORIA: Resident Medical Officer.
THE BRISBANE AND SOUTH COAST HOSPITALS BOARD: Honorary Vacancies.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table, without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 21, Elizabeth Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company, Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Members accepting apopintments as medical officers of country hospitals in Queensland are advised to submit a copy of their agreement to the Council before signing. Brisbane United Friendly Society Institute. Mount Isa Hospital.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	All Lodge Appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 65, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (Wellington Division): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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